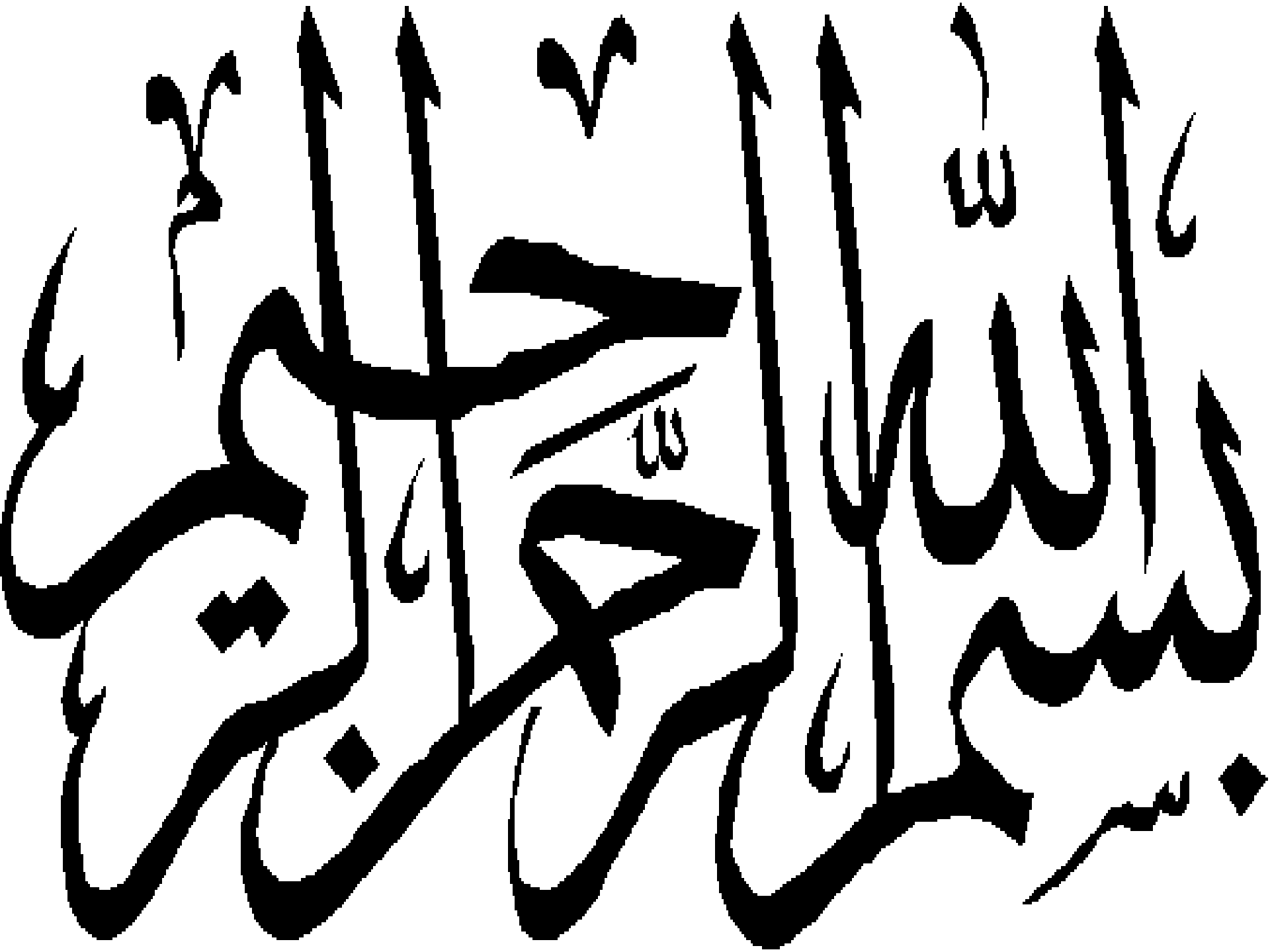
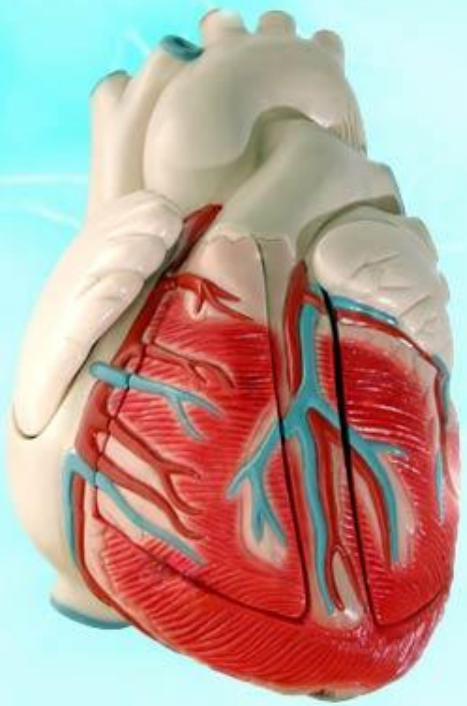
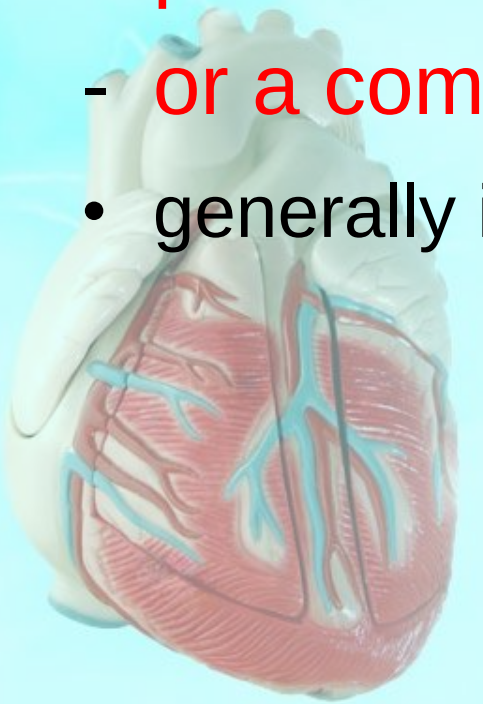




Pulmonary Hypertension

Dr.Hamidreza javadi
MD Cardiologist

- Abnormal elevation in PAP,result of:
- left heart failure,
- pulmonary parenchymal disease
- pulmonary vascular disease,
- pulmonary thromboembolism,
- or a combination of these factors.
- generally is a feature of advanced disease.

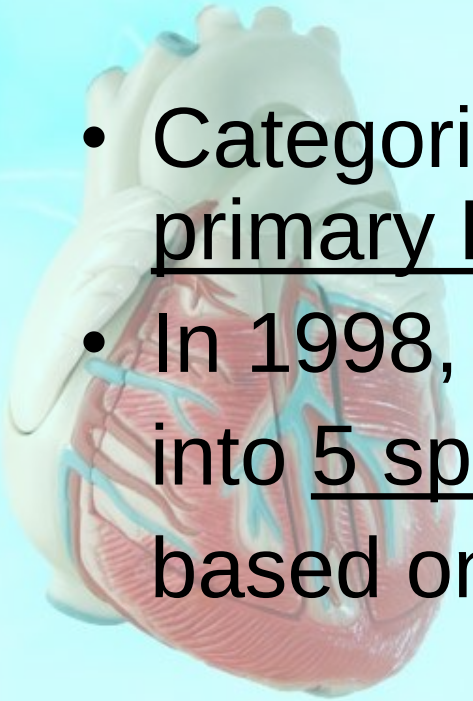


Pulmonary Hypertension Overview

- Defined as:

-mean PAP > 25mm Hg at rest

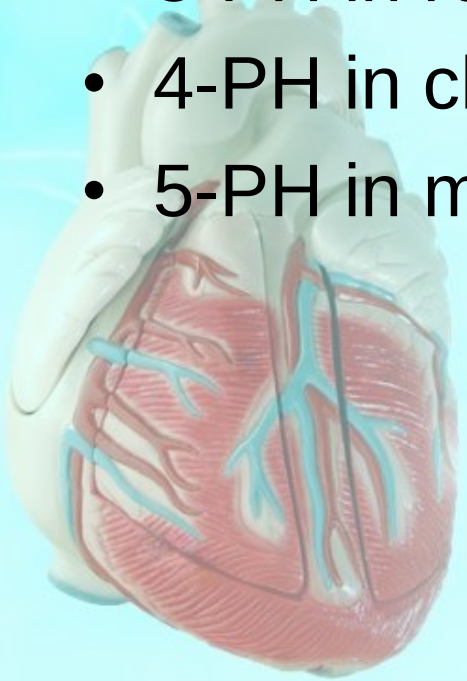
-or >30mm Hg with exertion



- Categorized by WHO in 1973 into just primary PH vs. secondary PH
- In 1998, WHO reclassified disease into 5 specific sub-categories based on specific disease process.

NEW CLASSIFICATION

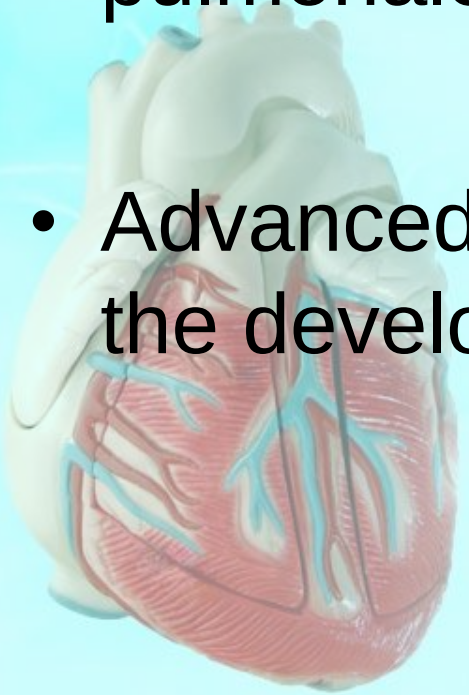
- 1-PAH; idiopathic, familial, dis. & drug associated, PVOD & PCH, persistant new born PH.
- 2-PH in left heart dis.
- 3-PH in respiratory dis.
- 4-PH in chronic thromboembolic dis.
- 5-PH in miscellaneous condition.



- Etiology underlying the PH be clearly determined before starting treatment.

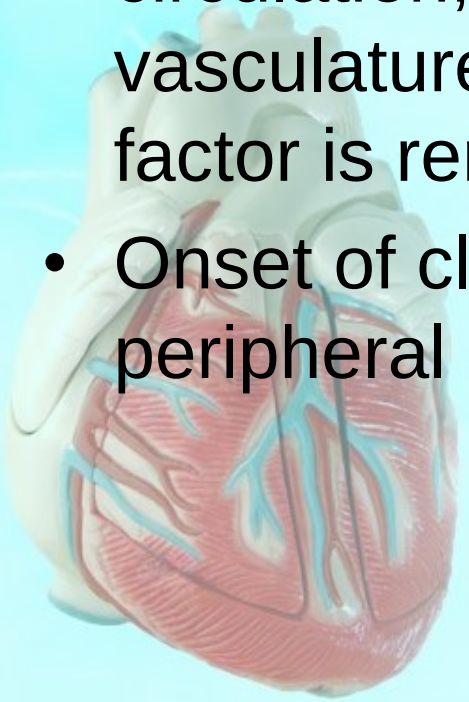
- PH is the most common cause of cor pulmonale.

- Advanced cor pulmonale is associated with the development of RV failure.



Pathophysiology

- The RV responds to an increase in resistance within the pulmonary circulation by increasing RVSP to preserve CO.
- Over time, chronic changes occur in the pulmonary circulation, result in progressive remodeling of the vasculature, can sustain PH, even if the initiating factor is removed.
- Onset of clinical RV failure, usually manifest by peripheral edema, associated with a poor outcome.



Diagnosis

- Symptom:
- Most common symptom is DOE.
- Other common symptoms:

-fatigue,

-CP that may represent RV ischemia,

-syncope,

-near syncope,

-and peripheral edema.

- Physical examination:

-increased JVP,

-reduced carotid pulse,

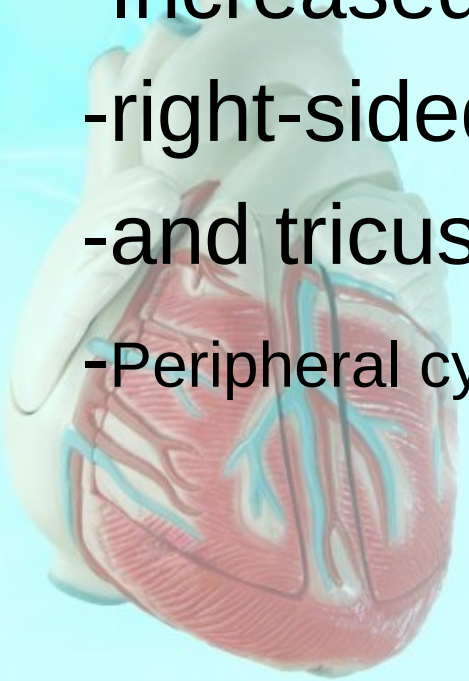
-palpable RV impulse.

-Increased pulmonic component of the S2,

-right-sided S4,

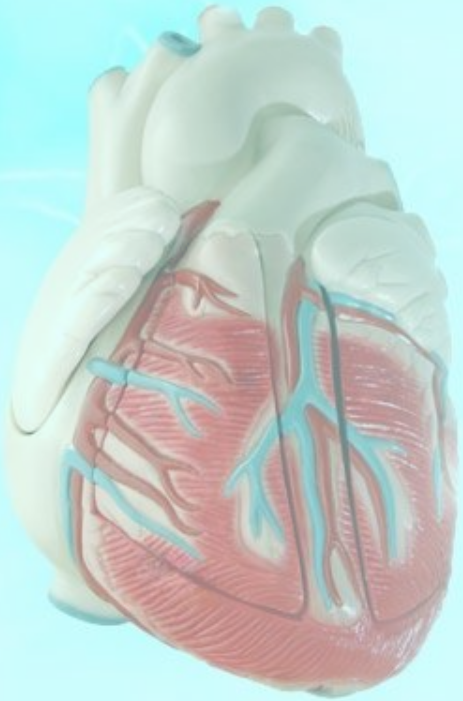
-and tricuspid regurgitation.

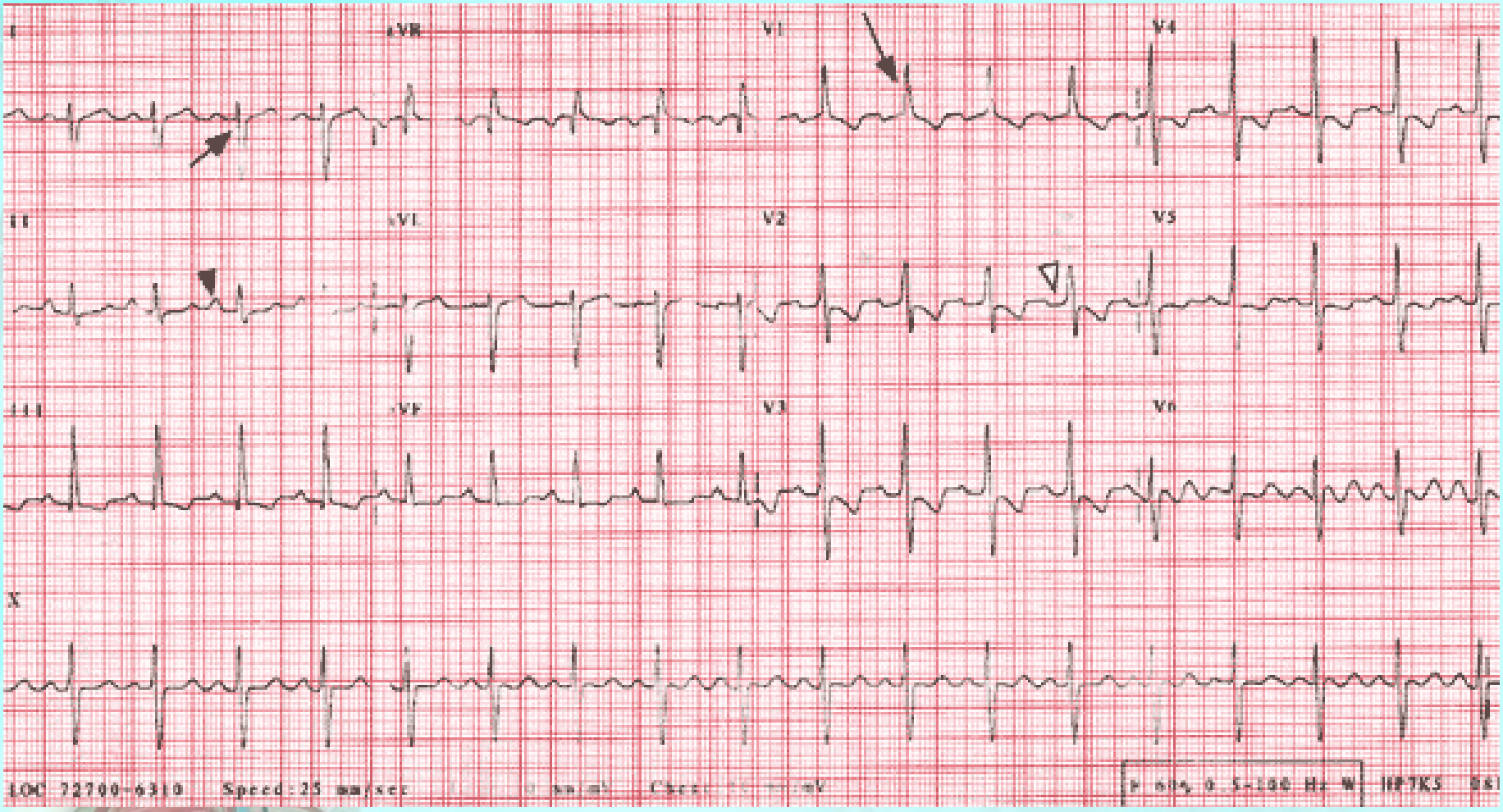
-Peripheral cyanosis and/or edema occur in later stages.



Chest X-Ray

The chest x-ray generally shows enlarged central pulmonary arteries. The lung fields may or may not reveal other pathology. One of the things the physician will check is whether the right side of the heart is enlarged.





ECG demonstrating the changes of RVH *(long arrow)* with strain in a patient with PPH. Right axis deviation *(short arrow)*, increased P-wave amplitude in lead II *(black arrowhead)*, and incomplete RBBB *(white arrowhead)* are highly specific but lack sensitivity for the detection of RVH.

Screening and diagnosis in PAH

Awareness + Screening
High risk populations

Key to early diagnosis

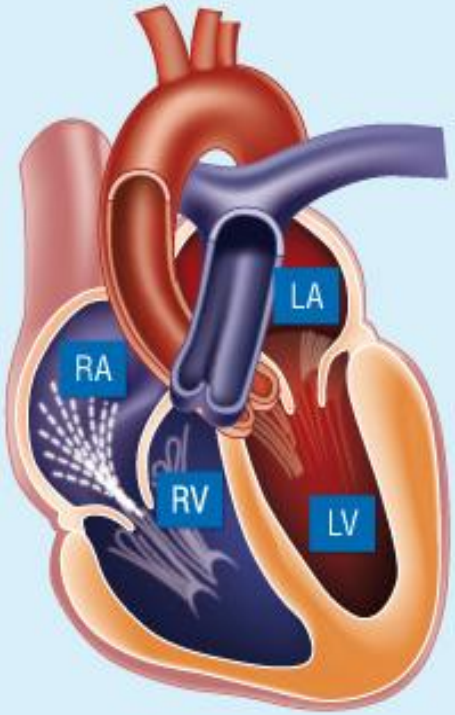
ECHOCARDIOGRAPHY

- RV enlargement
- Decreased LV cavity size
- Abnormal septal configuration consistent with RV overload
- Marked dependence on atrial systole for ventricular filling

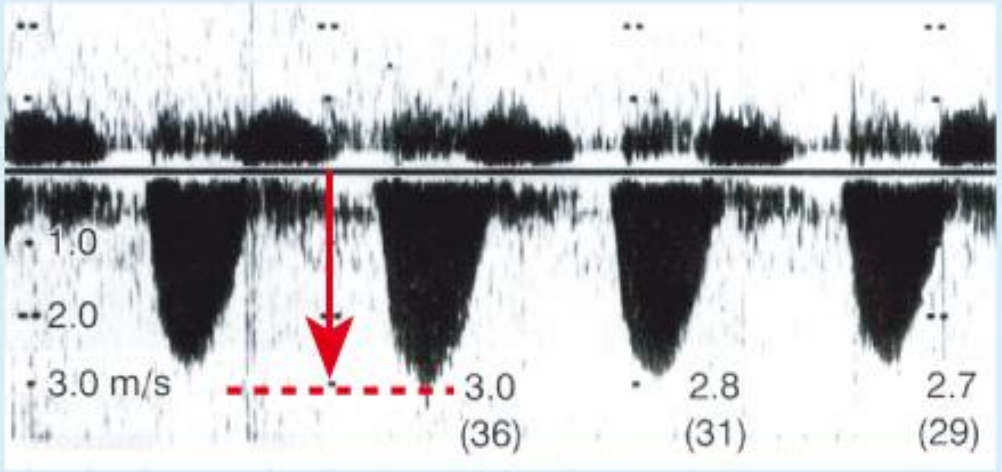
Right Heart Catheterisation
Mandatory to confirm and characterise disease

Adapted from Harrison's Principles of Internal Medicine, 14th ed.

Echocardiography in PAH



Tricuspid regurgitation (TR)



TR jet velocity (v)

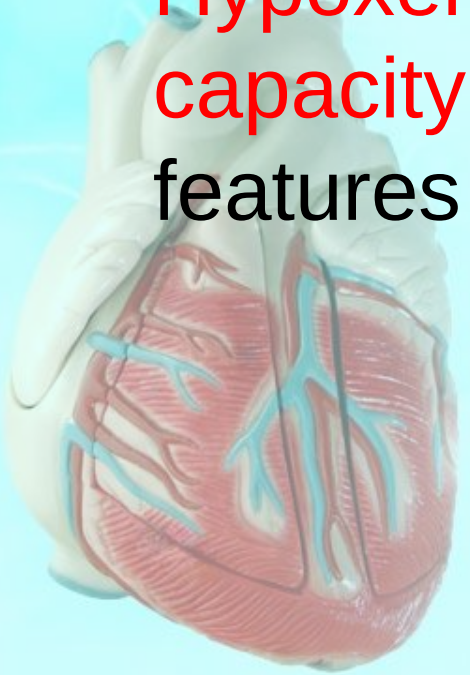
Syst PAP= Right Ventricular Systolic Pressure

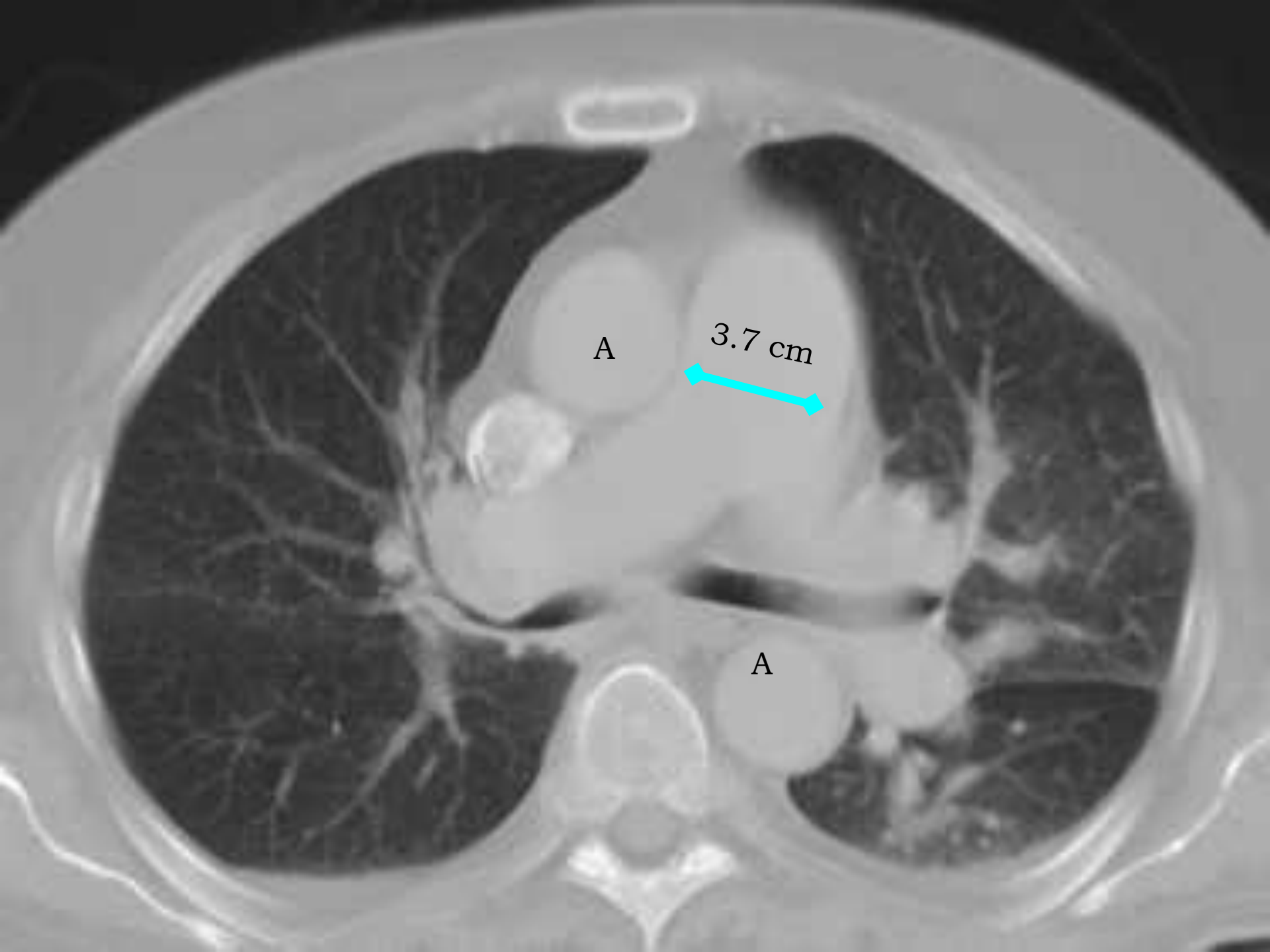
(in absence of pulmonary outflow obstruction)

$RVSP = 4v^2 + RAP^*$

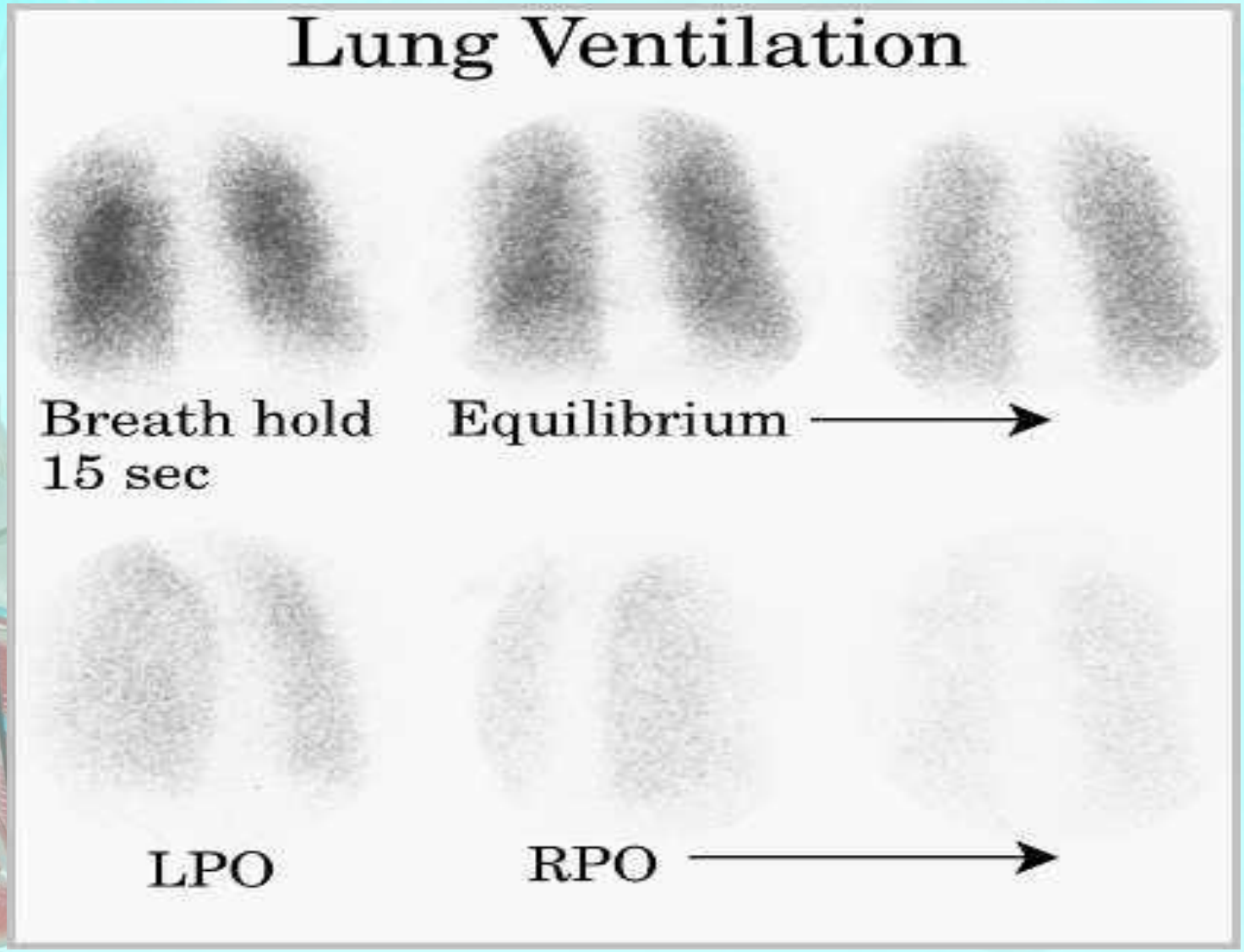
*ESC guidelines. Eur Heart J 2004 Dec;25(24):2243–78.

- Pulmonary function tests are helpful in documenting underlying obstructive airways disease,
- High-resolution chest CT is preferred to diagnose restrictive lung disease.
- Hypoxemia and an abnormal diffusing capacity for carbon monoxide are common features of PH of many causes.

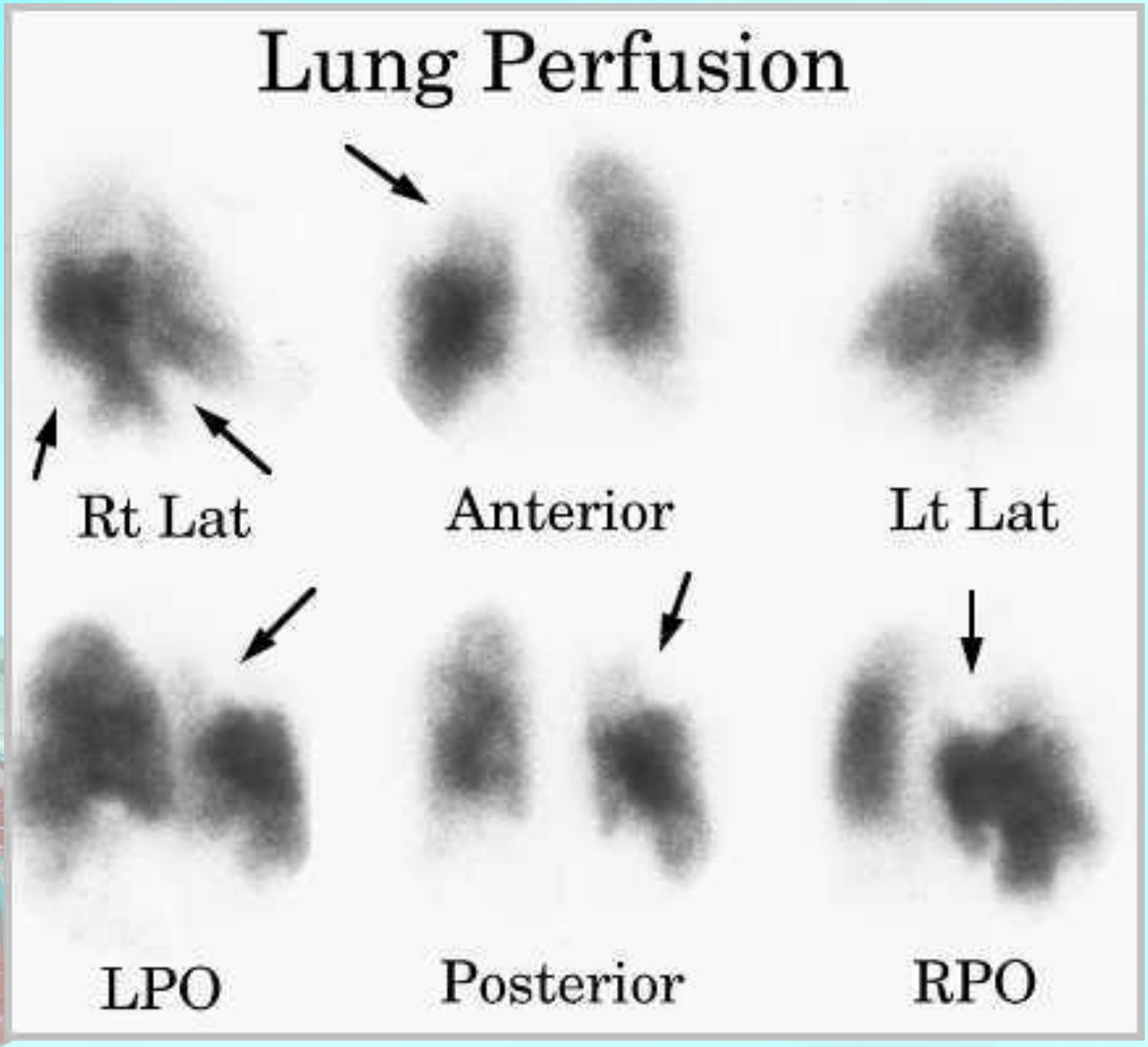



A
3.7 cm
A

A perfusion lung scan is almost always abnormal in patients with thromboembolic PH.



Lung Perfusion

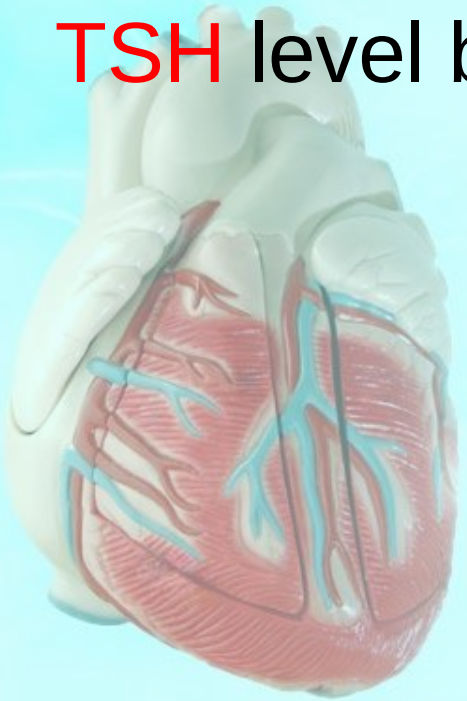


- Laboratory tests should include

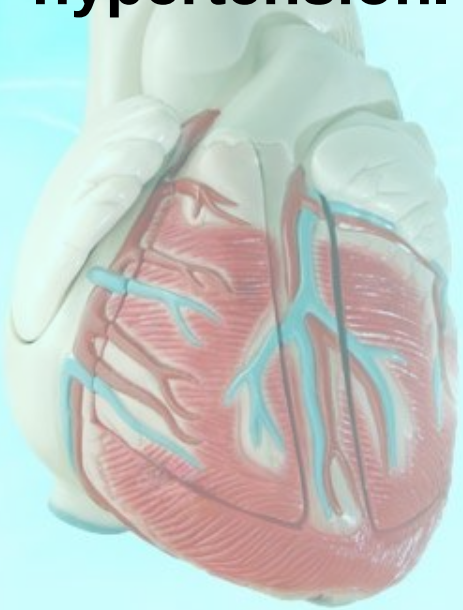
antinuclear antibody and HIV testing.

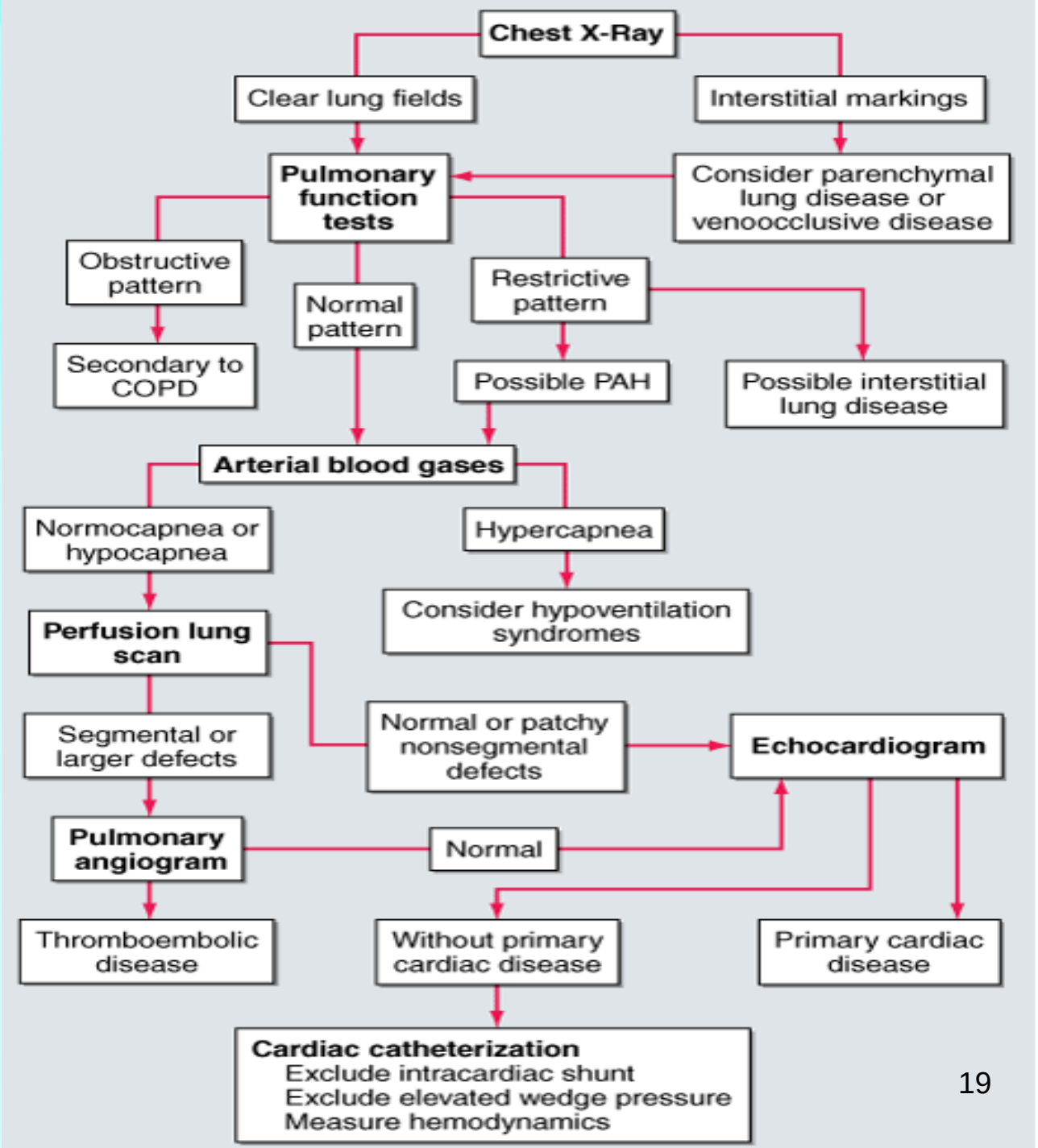
- Because of the high frequency of thyroid abnormalities in idiopathic PH,

TSH level be determined periodically.



An algorithm for the workup of a patient with unexplained pulmonary hypertension.

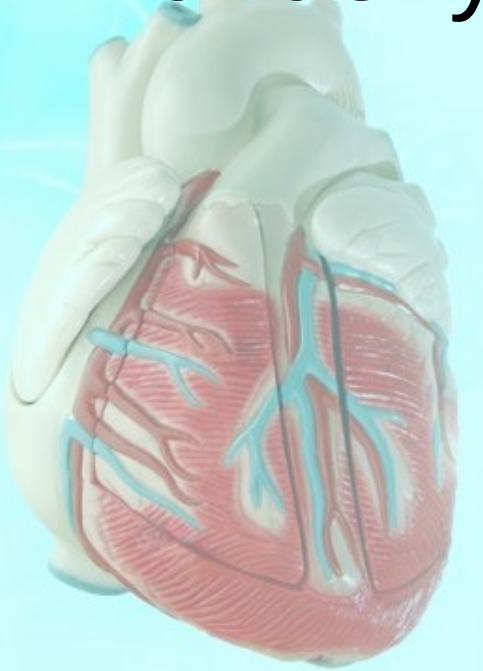




Cardiac Catheterization

- For accurate measurement of:

PAP, CO, and LV filling pressure, as well as for exclusion of an underlying cardiac shunt.



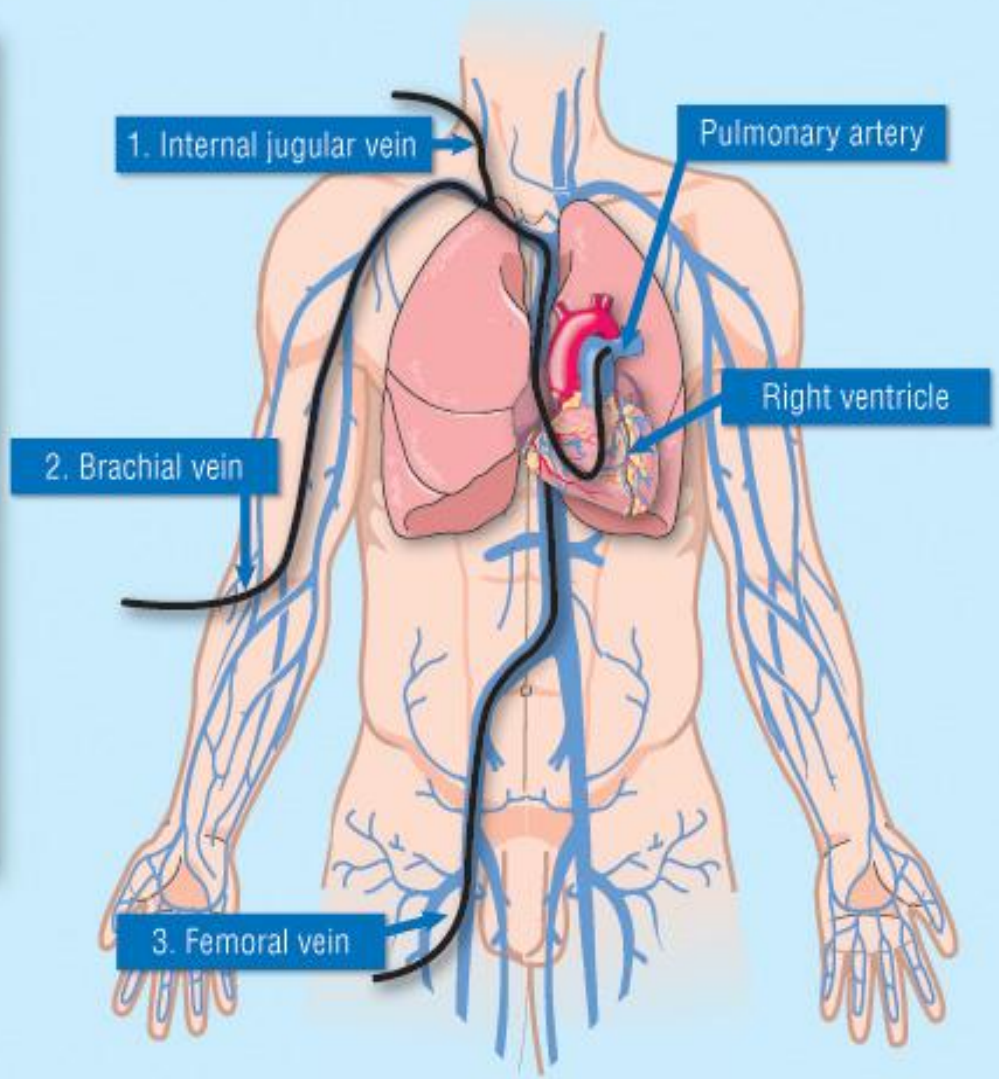
Right Heart Catheterisation

Right heart catheterisation is required to confirm the diagnosis of PAH.

PAH is defined by

- mPAP > 25 mmHg at rest
- mPAP > 30 mmHg with exercise
- PCWP < 15 mmHg
- PVR > 3 units

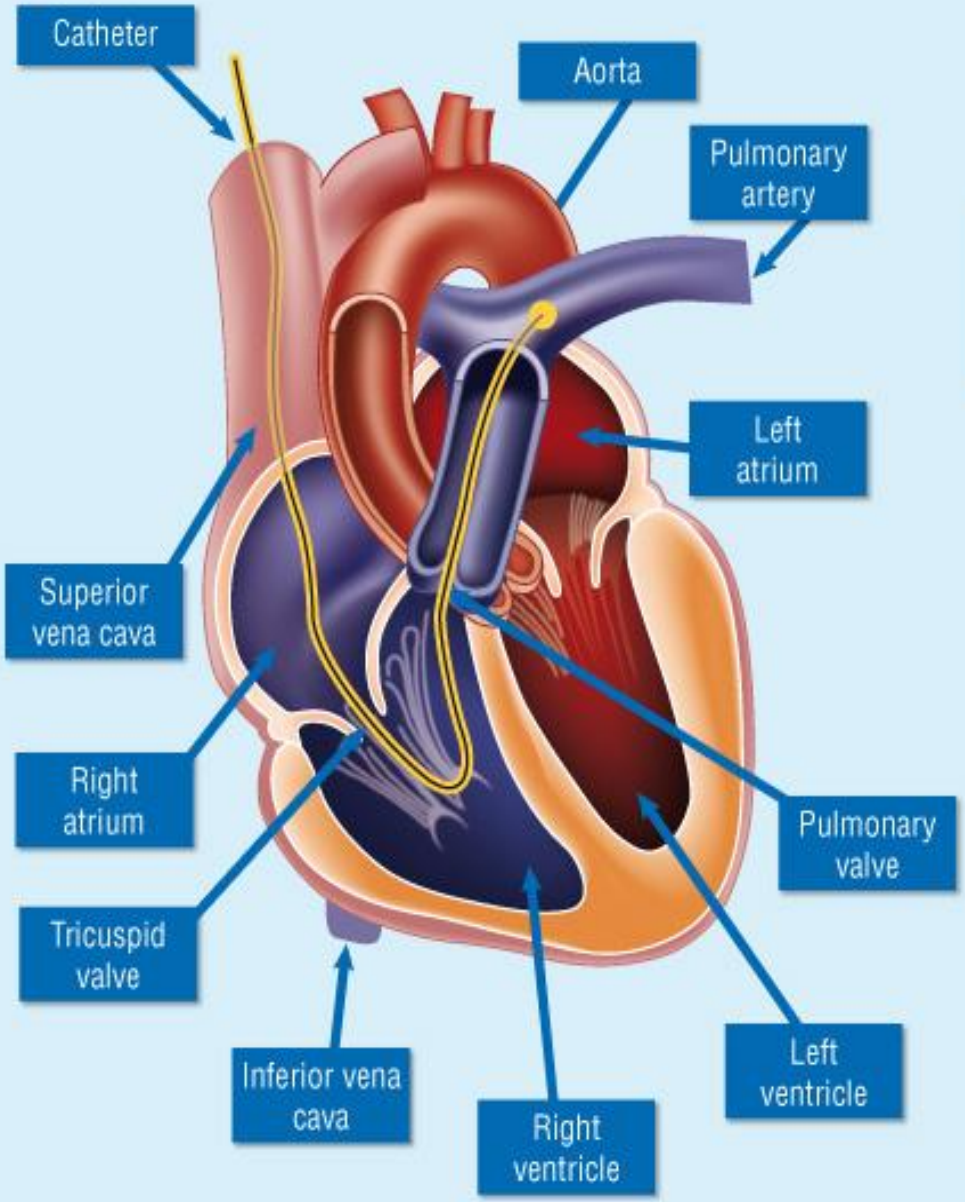
Cardiac output is also required to calculate PVR.



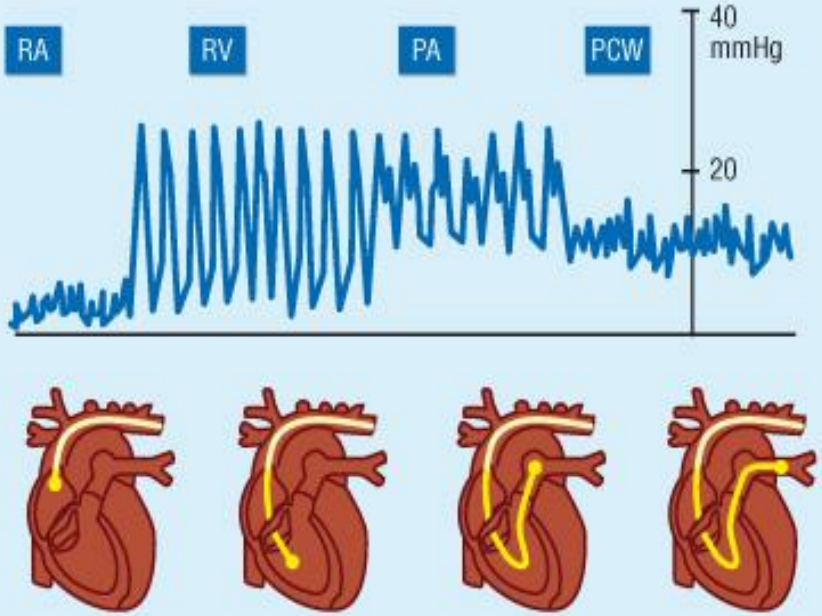
Standard approaches for catheter access

Barst, JACC 2004 vol.43 N. 12

Right Heart Catheterisation



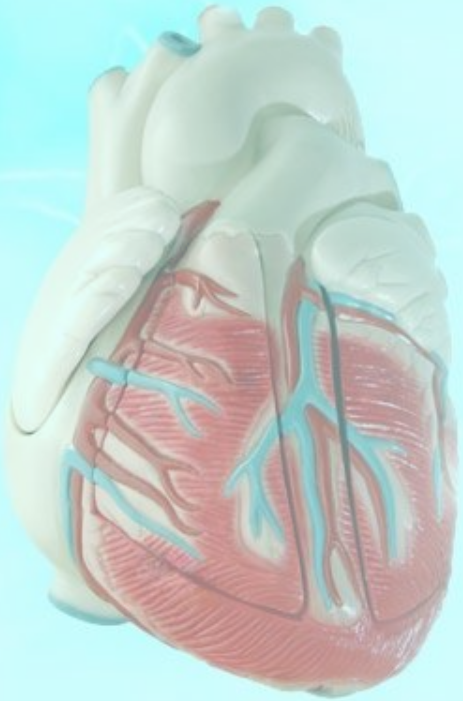
Characteristic intracardiac pressure waveforms during passage through the heart

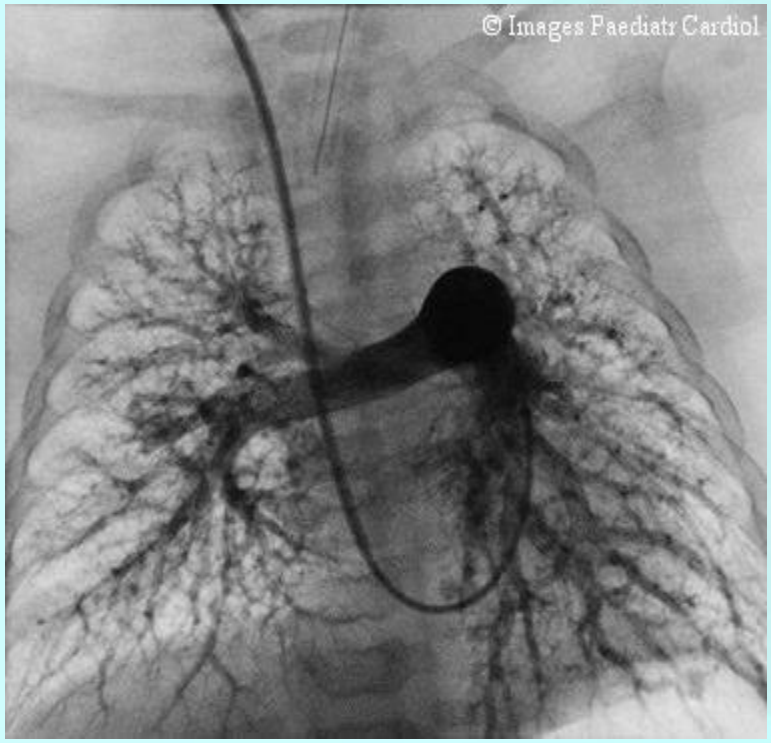


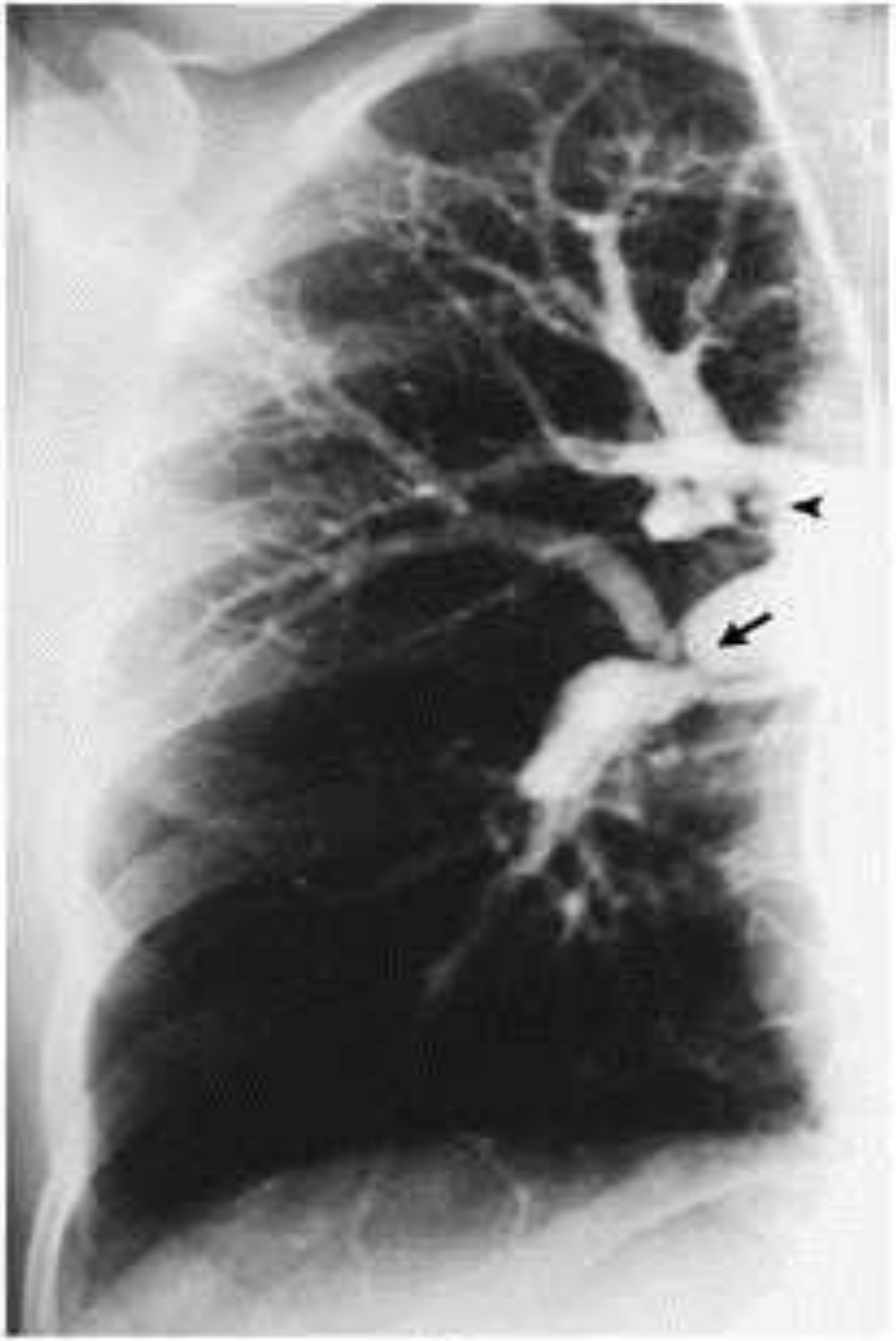
Pulmonary Angiogram

Used to measure circulation in the lungs and to visualize clots in the lung on x-rays. The test involves insertion of a thin catheter into the pulmonary artery through which an iodine dye is injected.

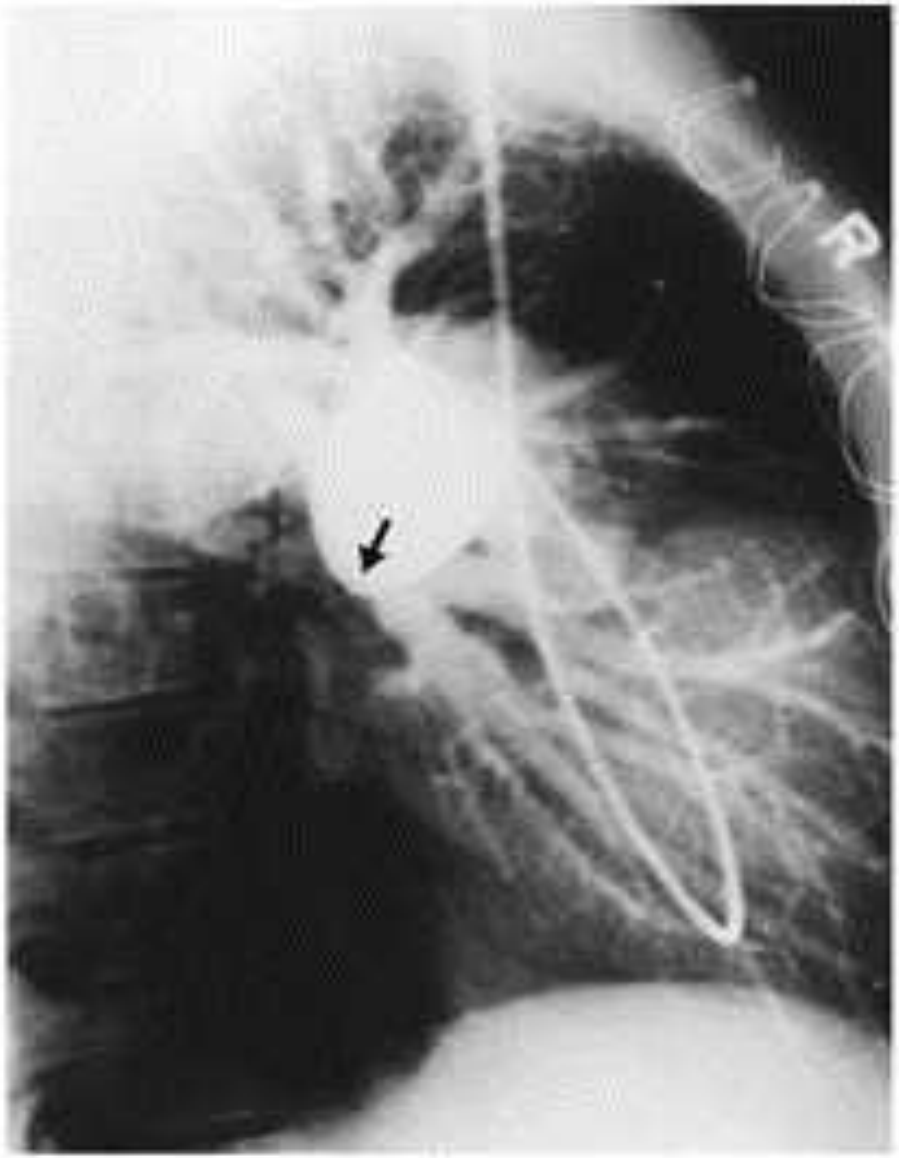
Image of any blood clots present in the lung can be observed and circulation of blood through lung's blood vessels can be tracked.







A

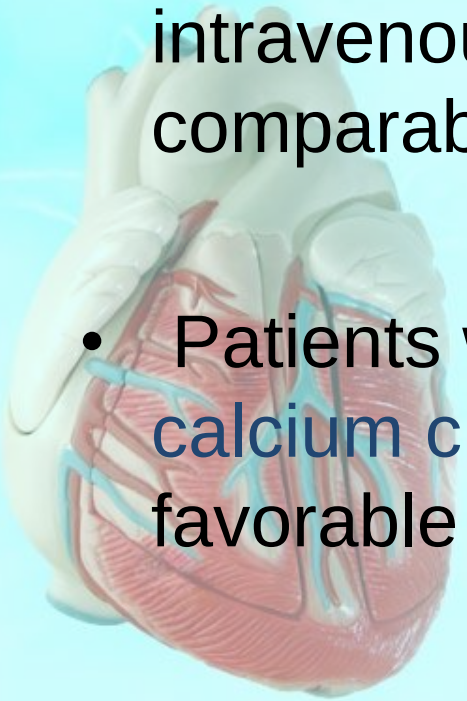


B

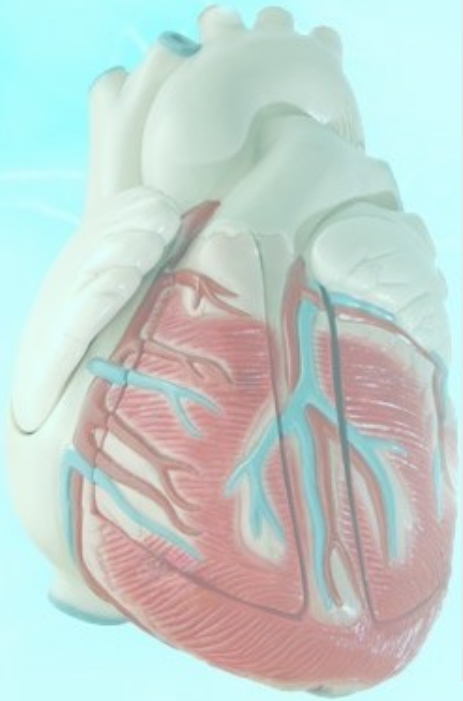
- Patients with PH should undergo drug testing with a short-acting pulmonary vasodilator at the time of cardiac catheterization to determine the extent of pulmonary vasodilator reactivity .

- Inhaled nitric oxide, intravenous adenosine, and intravenous epoprostenol appear to have comparable effects in reducing PAP acutely.

- Patients who respond can often be treated with calcium channel blockers and have a more favorable prognosis.



An algorithm for the selection of optimal drug treatment of a patient with pulmonary arterial hypertension.



ALGORITHM FOR DRUG TREATMENT SELECTION

Acute drug testing
Adenosine
Epoprostenol
Nitric oxide

Marked reduction in pulmonary artery pressure

Trial of *calcium blockers*

Response

Chronic therapy

No response

Minimal reduction in pulmonary artery pressure

Functional Class II-III

Bosentan
Sildenafil
Iloprost

Response

Chronic therapy

No response

Functional Class III-IV

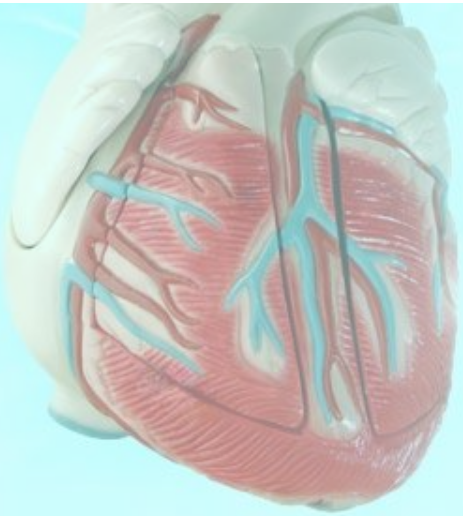
Epoprostenol
Treprostinil

classification

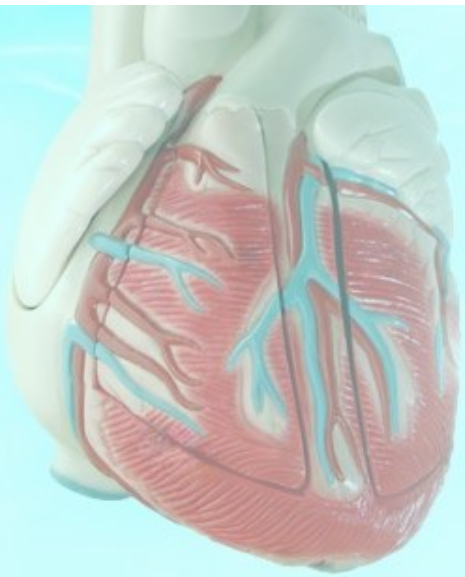
1. PAH
   - A-Idiopathic PAH
   - B-Familial PAH
   - C-Associated with:
     - Connective tissue disease
     - CHD (shunts)
     - Portal hypertension
     - HIV infection
     - Sickle cell disease
     - Drugs and toxins
     - Other
   - D-Associated with significant venous or capillary involvement(PVOD,PCH)
   - E-Persistent PH of the newborn
2. PH associated with left heart disease
3. PH associated with respiratory disease
   - COPD
   - Interstitial lung diseases
4. PH due to chronic thrombotic and/or embolic disease
5. Miscellaneous

1. Simonneau G *et al. JACC* 2004

2. Pulmonary hypertension with left heart disease
2.1. Left-sided atrial or ventricular heart disease
2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Sleep-disordered breathing
3.4. Alveolar hypoventilation disorders
3.5. Chronic exposure to high altitude
3.6. Developmental abnormalities



4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
4.1. Thromboembolic obstruction of proximal pulmonary arteries
4.2. Thromboembolic obstruction of distal pulmonary arteries
4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)



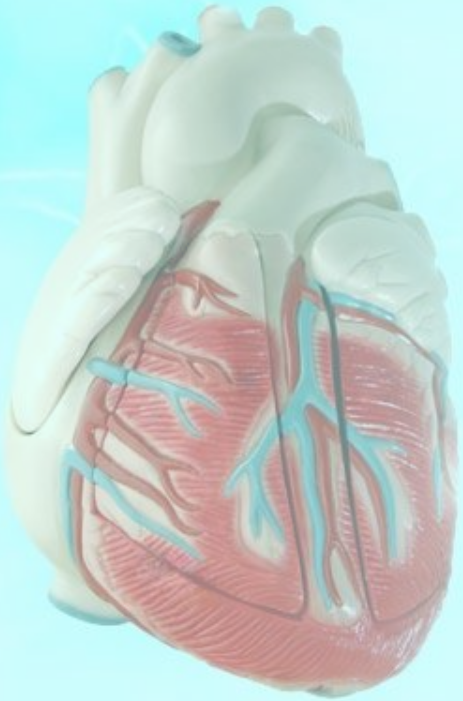
GROUP 1
Pulmonary Arterial Hypertension

- There are many causes of pulmonary arterial hypertension (PAH).
- Patients with PAH share a common histopathology characterized by

- medial hypertrophy,
- eccentric and concentric intimal fibrosis,
- recanalized thrombi appearing as fibrous webs,
- and plexiform lesions.

Pathobiology

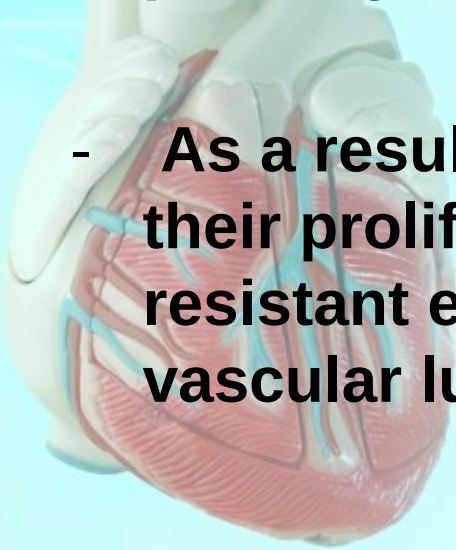
- Abnormalities in molecular pathways regulating the pulmonary vascular endothelial and smooth-muscle cells have been described as underlying PAH.



- **These include:**

- **inhibition of the voltage-regulated K. channel,**
- **mutations in the bone morphogenetic protein-2 receptor,**
- **increased serotonin uptake in the SMCs,**
- **increased angiopoietin expression in the SMCs,**
- **and excessive thrombin deposition related to a procoagulant state.**

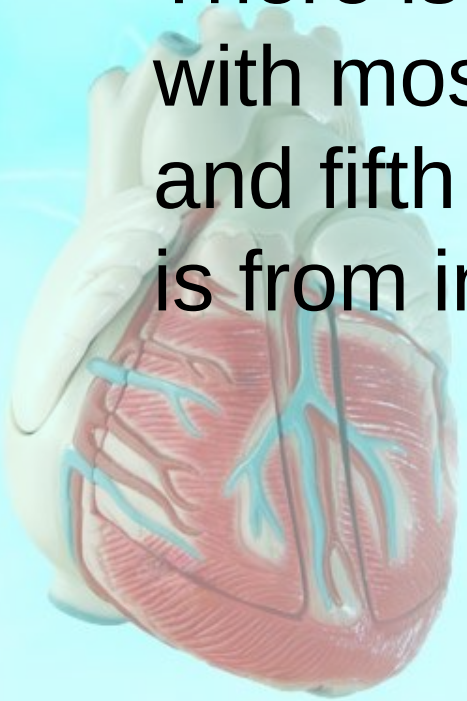
- **As a result loss of apoptosis of the SMCs, allowing their proliferation, and emergence of apoptosis-resistant endothelial cells which can obliterate the vascular lumen.**



A-Idiopathic Pulmonary Arterial Hypertension

- PPH is uncommon, with an estimated incidence of two cases per million.

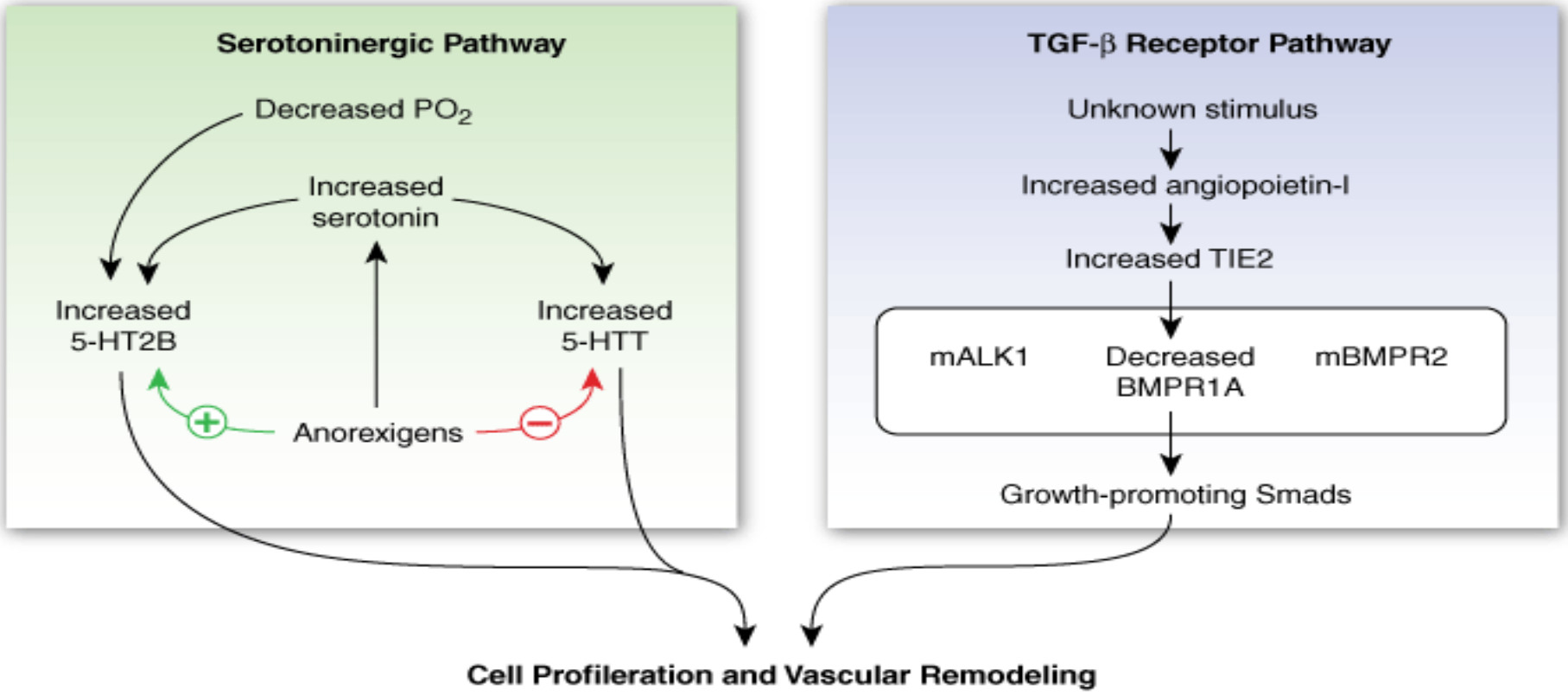
- There is a strong female predominance, with most patients presenting in the fourth and fifth decades, although the age range is from infancy to >60 years.



- B-Familial IPAH accounts for up to 20% of cases of IPAH and is characterized by autosomal dominant inheritance, variable age of onset, and incomplete penetrance.

- The clinical and pathologic features of familial and sporadic IPAH are identical.

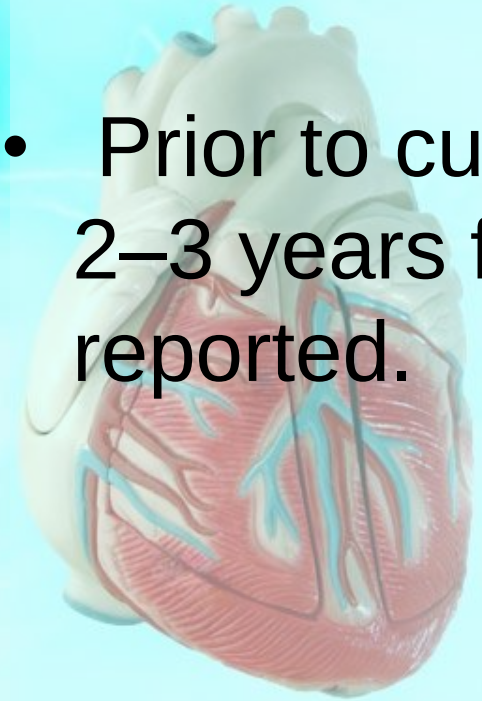
- Heterozygous germline mutations that involve the gene coding the type II bone morphogenetic protein receptor (BMPR II), a member of the transforming growth factor (TGF) superfamily, appear to account for most cases of familial IPAH.



Mechanistic pathways promoting pulmonary arterial hypertension (PAH). External stimuli, such as hypoxia or anorexigens, can stimulate a serotoninergic pathway which, in concert with internal stimuli involving the TGF-$^{\beta}$ receptor pathway can produce PAH.
5-HT2B, serotonin receptor; 5-HTT, serotonin transporter;
TGF-$^{\beta}$, transforming growth factor $^{\beta}$; TIE2, angiopoietein-1 receptor;
BMPR1A, bone morphogenetic protein receptor 1A;
mBMPR2, mutant form of bone morphogenetic protein receptor 2;
mALK1, activin-receptor-like kinase.

Natural History

- The natural history of IPAH is uncertain,
- because the predominant symptom is dyspnea, with insidious onset, the disease is typically diagnosed late in its course.



- Prior to current therapies, a mean survival of 2–3 years from the time of diagnosis was reported.

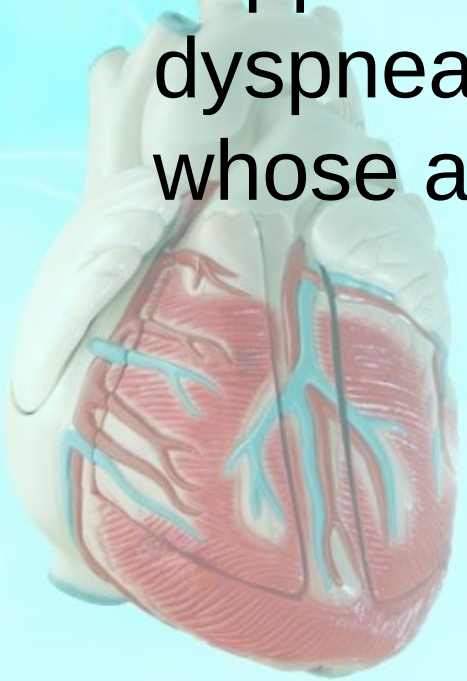
- Functional class remains a strong predictor of survival, with NYHA FC IV having a mean survival of <6 months.

- The cause of death is usually RV failure, manifest by progressive hypoxemia, tachycardia, hypotension, and edema.

Treatment

- PAH refers to a variety of diseases, which includes idiopathic (I)PAH.
- Several treatments for PAH have approved.
- 1- patients should be cautioned against participating in activities that demand increased physical stress.

- 2-Diuretic therapy relieves peripheral edema and may be useful in reducing RV volume overload in the presence of TR.
- 3-Resting and exercise pulse oximetry should be obtained, as O_2 supplementation helps to alleviate dyspnea and RV ischemia in patients whose arterial O_2 saturation is reduced.

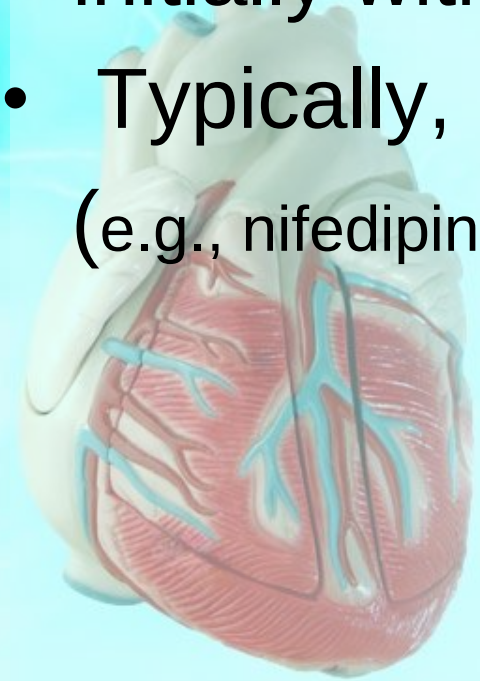


- 4- Anticoagulant therapy for all patients with PAH based on retrospective and prospective studies demonstrating that warfarin increases survival of PAH patients.

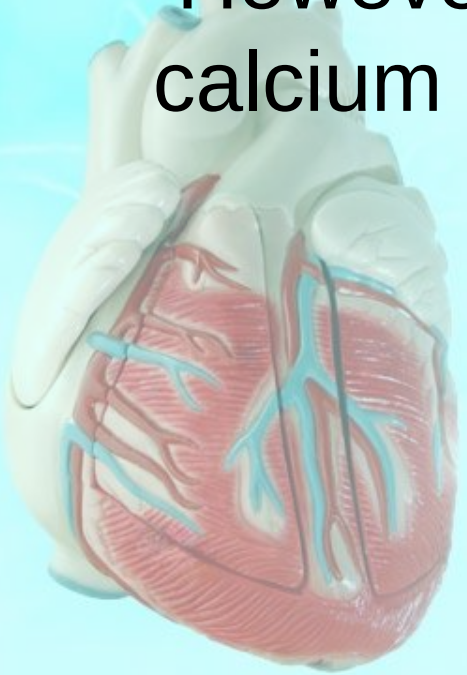
- The dose of warfarin is generally titrated to achieve an INR of 2–3 times control.

5-Calcium Channel Blockers

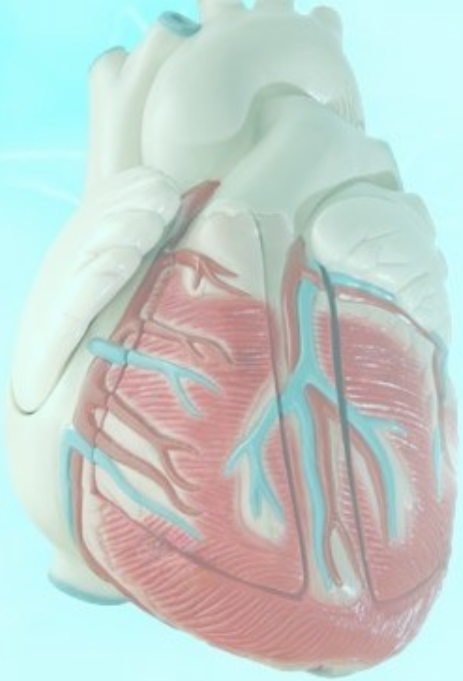
- Patients who have substantial reductions in PAP in response to short-acting vasodilators at cardiac catheterization (a fall in mean PAP 10 mmHg and a final mean pressure <40 mmHg) should be treated initially with calcium channel blockers.
- Typically, patients require high doses (e.g., nifedipine, 240 mg/d, or amlodipine, 20 mg/d).



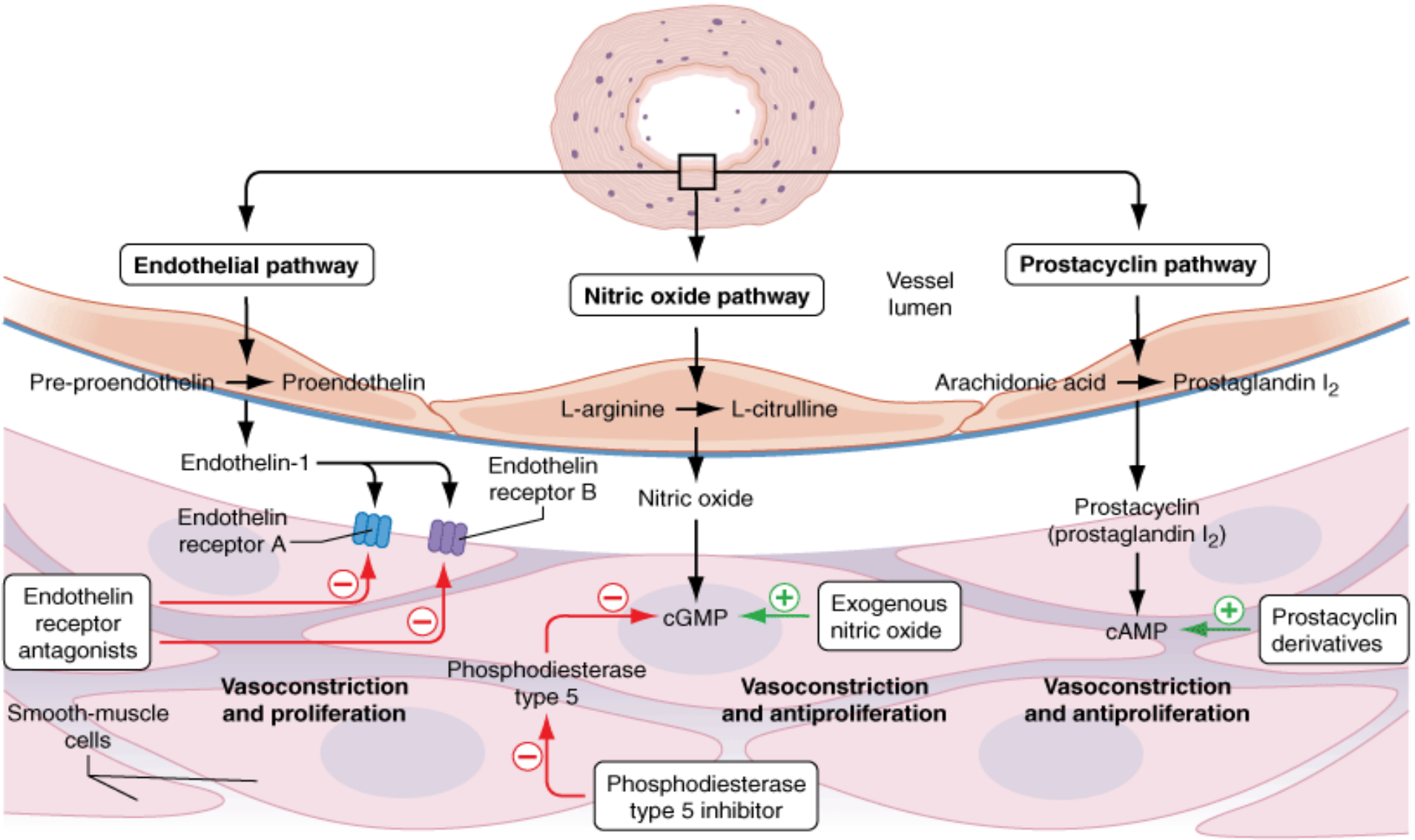
- Patients who respond favorably usually have dramatic reductions in PAP and PVR associated with improved symptoms, regression of RVH, and improved survival now documented to exceed 20 years.
- However, <20% of patients respond to calcium channel blockers in the long term.



- These drugs should not be given to patients who are unresponsive, as they can result in hypotension, hypoxemia, tachycardia, and worsening right heart failure.

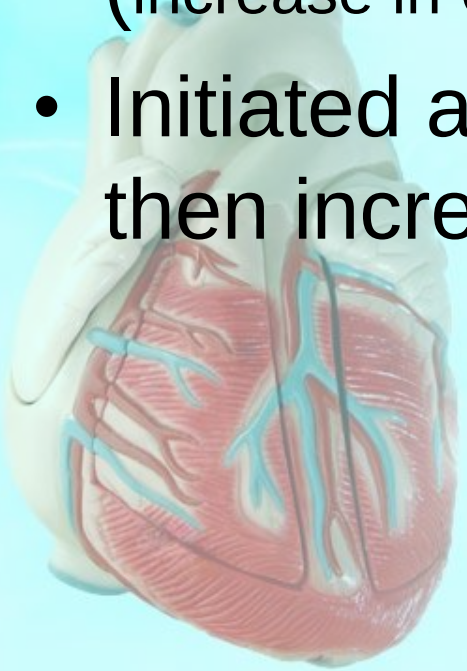


6- Current therapies target **multiple growth factor pathways** that appear to be involved in the pathogenesis of PAH.



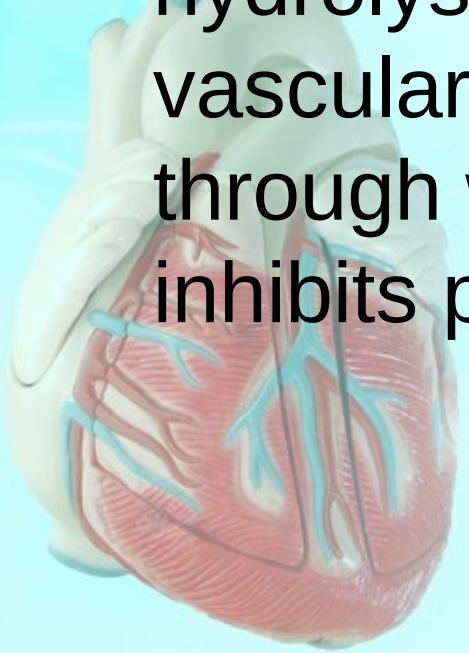
Endothelin Receptor Antagonists

- The nonselective endothelin receptor antagonist *bosentan* is an approved treatment of PAH for NYHA FC III and IV.
- Improve symptoms and exercise tolerance (increase in 6-min walking distance).
- Initiated at 62.5 mg bid for the first month and then increased to 125 mg bid.



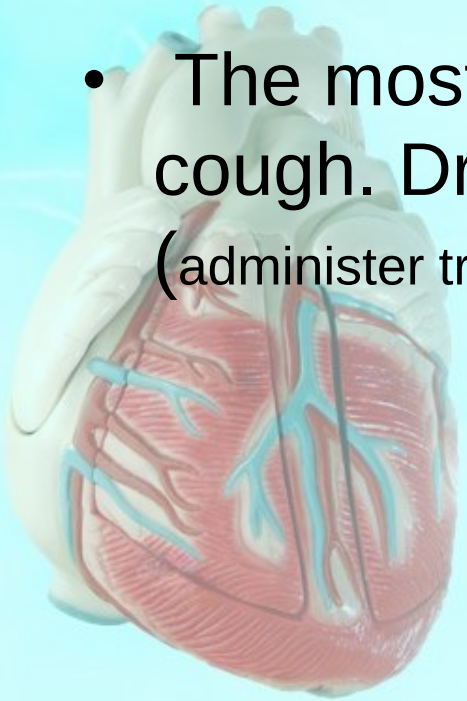
Phosphodiesterase-5 Inhibitors

- *Sildenafil*, a phosphodiesterase-5 inhibitor, is approved for the treatment of PAH in NYHA FC II and III.
- Phosphodiesterase-5 is responsible for the hydrolysis of cyclic GMP in pulmonary vascular smooth muscle, the mediator through which nitric oxide lowers PAP and inhibits pulmonary vascular growth.

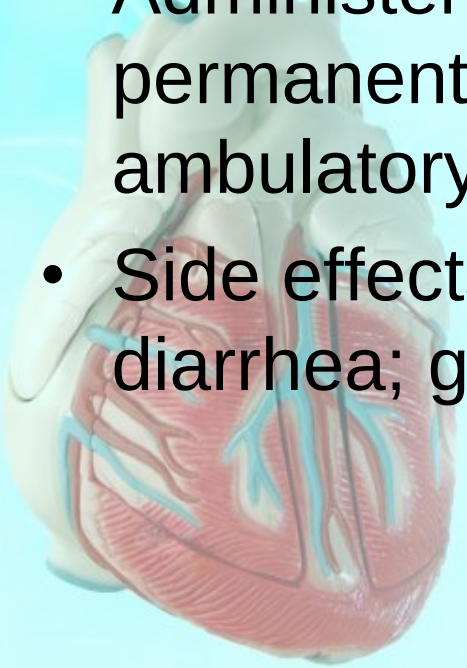


Prostacyclins

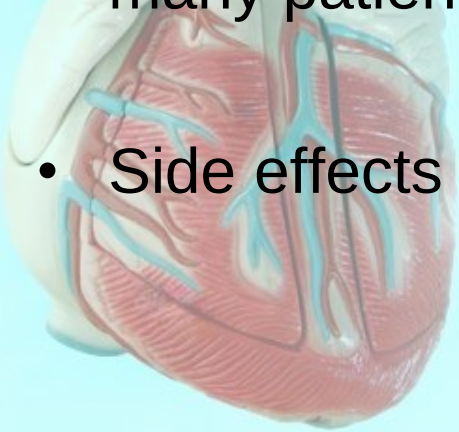
- *Iloprost,* a prostacyclin analogue, is approved via inhalation for PAH in NYHA FC III and IV.
- improve symptoms and exercise tolerance.
- Therapy can be given at either 2.5 or 5 mcg per inhalation treatment. (by a dedicated nebulizer).
- The most common side effects are flushing and cough. Drug is very short half-life (<30 min) (administer treatments as often as every 2 h).



- *Epoprostenol* is approved for the treatment of PAH in NYHA FC III or IV.
- Clinical trials have demonstrated an improvement in symptoms, exercise tolerance, and survival even if no acute hemodynamic response to drug challenge occurs.
- Administered IV and requires placement of a permanent CVP catheter and infusion through an ambulatory infusion pump.
- Side effects include flushing, jaw pain, and diarrhea; generally tolerated by most patients.



- *Treprostinil,* an analogue of epoprostenol, is approved for patients with PAH in NYHA FC II–IV.
- Treprostinil has a longer half-life than epoprostenol (4 h), is stable at room temperature, and may be given IV or subcutaneously through a small infusion pump that was originally developed for insulin.
- Demonstrated an improvement in symptoms and exercise capacity.
- The major problem with the subcutaneous administration has been local pain at the infusion site, which has caused many patients to discontinue therapy.
- Side effects are similar to those seen with epoprostenol.

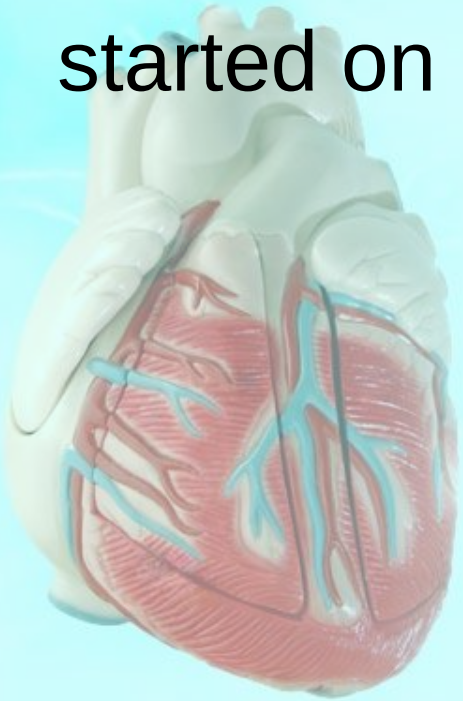


- Favorable properties of prostacyclins include vasodilation, platelet inhibition, inhibition of vascular smooth-muscle growth, and inotropic effects.

- Although most clinical trials have focused on patients with advanced symptoms, it is recommended that every patient diagnosed with PAH be treated.

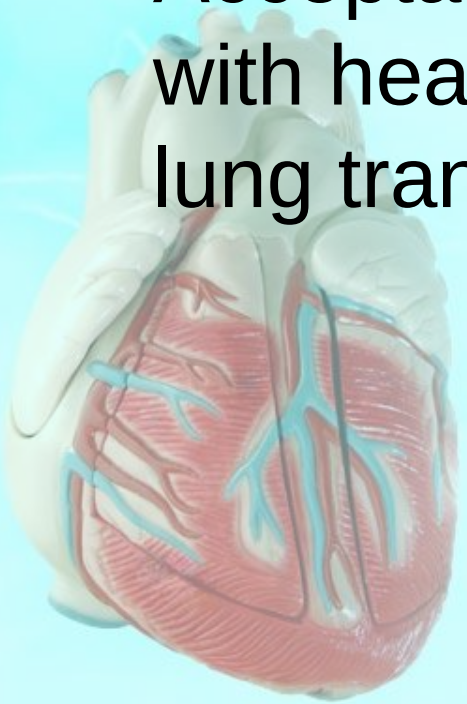
- In the trials using bosentan, sildenafil, and iloprost, full clinical benefit was generally manifest within the first 2 months of therapy.

- Patients who fail to adequately improve should have the treatment discontinued and started on a different therapy.

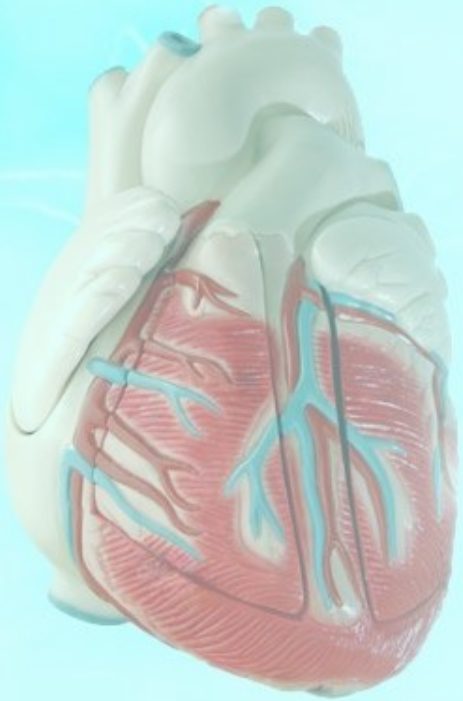


Lung Transplantation

- Lung transplantation is considered for patients who, while on an IV prostacyclin, continue to manifest RV HF.
- Acceptable results have been achieved with heart-lung, bilateral lung, and single-lung transplant.



C-Conditions Associated with PH



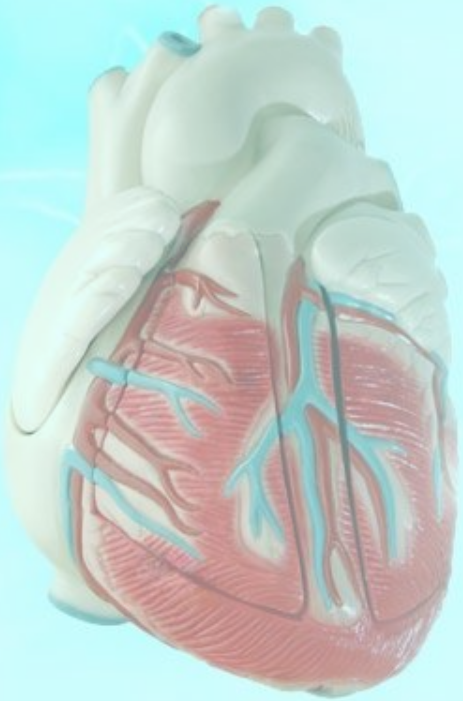
Collagen Vascular Disease

- All of the collagen vascular diseases may be associated with PAH.
- This complication occurs commonly with

-CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, and telangiectasia)

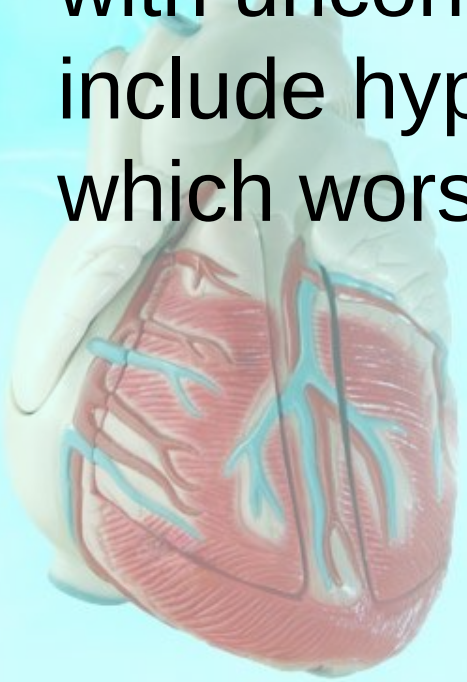
- scleroderma,
- less frequently in systemic lupus erythematosus,
- Sjögren's syndrome,
- dermatomyositis,
- polymyositis,
- and rheumatoid arthritis.

- Treatment of these patients is identical to that of patients with IPAH but is less effective.
- The treatment of the PH, however, does not affect the natural history of the underlying collagen vascular disease.



Congenital Systemic to Pulmonary Shunts

- It is common for large post-tricuspid cardiac shunts (e.g., VSD,PDA) to produce severe PAH.
- Less common, it may occur in pre-tricuspid shunts (e.g., ASD, anomalous pulmonary venous drainage).
- with uncorrected shunts, the clinical features include hypoxemia and peripheral cyanosis, which worsen dramatically with exertion.



- PAH may occur years or even decades after surgical correction of these lesions, in which case there will be no associated right-to-left shunting.
- These patients present similarly to patients with IPAH but tend to have better long-term survival.
- The treatments are similar to those for IPAH.

Portal Hypertension

- Portal hypertension is associated with PAH, but the mechanism remains unknown.
- The etiology of ascites and edema can be confusing; can have both cardiac and hepatic causes.
- Patients with mild PH who have a favorable response to epoprostenol have undergone successful liver transplantation with improvement of the pulmonary vascular dis.

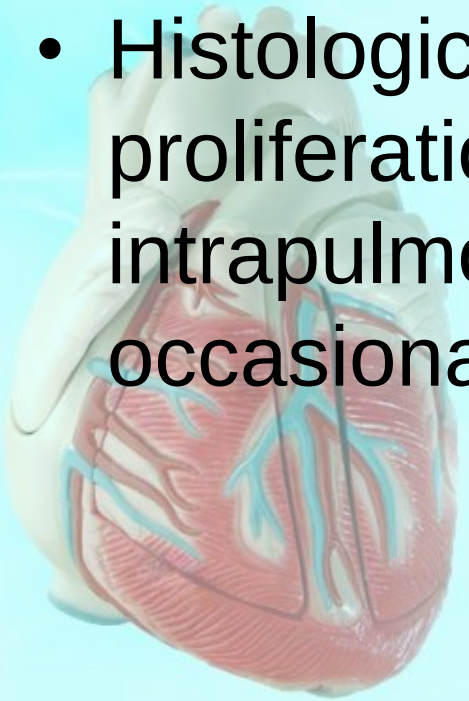
Anorexigens

- A causal relationship has been established between exposure to several anorexigens, including aminorex and the fenfluramines, and the development of PAH.
- Often the PH will not develop until years after the last exposure.
- Clinical features are identical to those of IPAH, the patients appear to be less responsive to medical treatments and have a poorer prognosis.

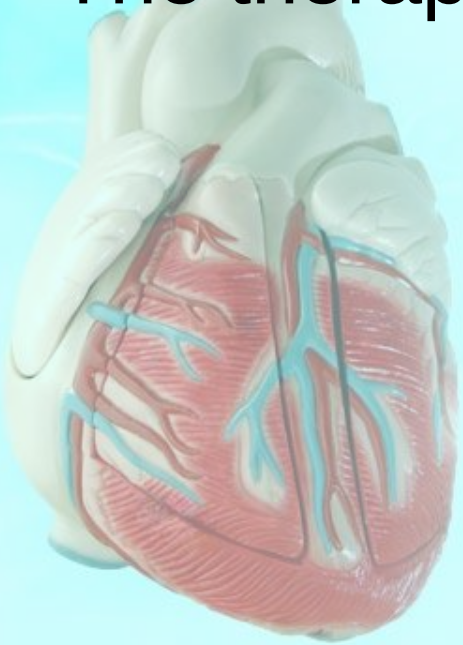
D-Pulmonary Venoocclusive Disease

- Pulmonary venoocclusive disease is a rare and distinct pathologic entity found in <10% of patients who present with unexplained PH.

- Histologically it is manifest by intimal proliferation and fibrosis of the intrapulmonary veins and venules, occasionally extending to the arteriolar bed.



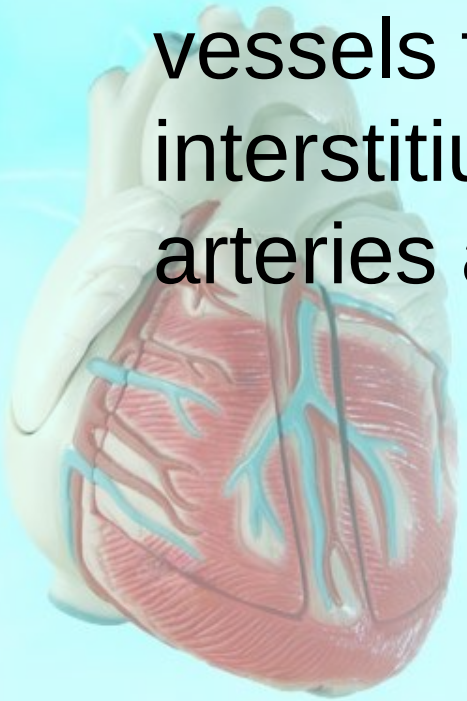
- The pulmonary venous obstruction explains the increase in PCWP observed in patients with advanced disease.
- These patients may develop orthopnea that can mimic LV failure.
- The therapy of this condition is not established.



D-Pulmonary Capillary Hemangiomatosis

- A very rare form of PAH.

- Histologically it is characterized by the presence of infiltrating thin-walled blood vessels throughout the pulmonary interstitium and walls of the pulmonary arteries and veins.



- Symptoms are usually those of IPAH but often with hemoptysis as a clinical feature.

- The diagnosis can be made with pulmonary angiography.
- The clinical course is usually one of progressive deterioration leading to death.
- There is no established therapy.

GROUP II
Pulmonary Venous Hypertension
(PH associated with left heart disease)

- PH occurs as a result of increased resistance to pulmonary venous drainage.
- It is often associated with:

-diastolic LV dysfunction;

-diseases of pericard, or mitral or aortic valves;

- or rare entities such as:

-cor triatriatum,

-left atrial myxoma,

-extrinsic compression of the central pulmonary veins from fibrosing mediastinitis,

and pulmonary venoocclusive disease.

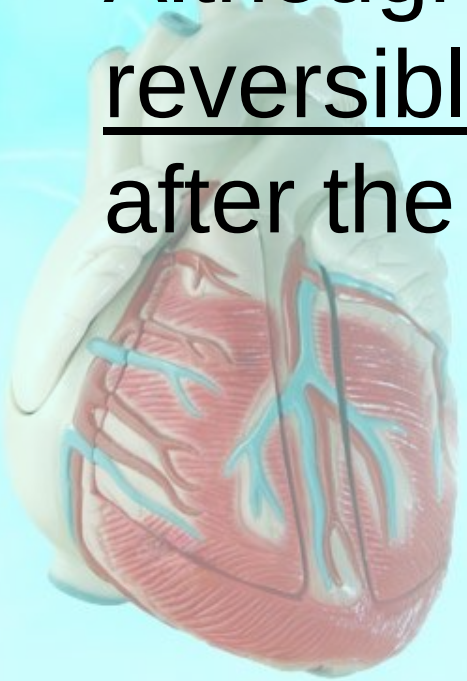
- Microcirculatory lesions include

-capillary congestion,

-focal alveolar edema,

-dilatation of the interstitial lymphatics.

- Although these lesions are potentially reversible, regression may take years after the underlying cause is removed.



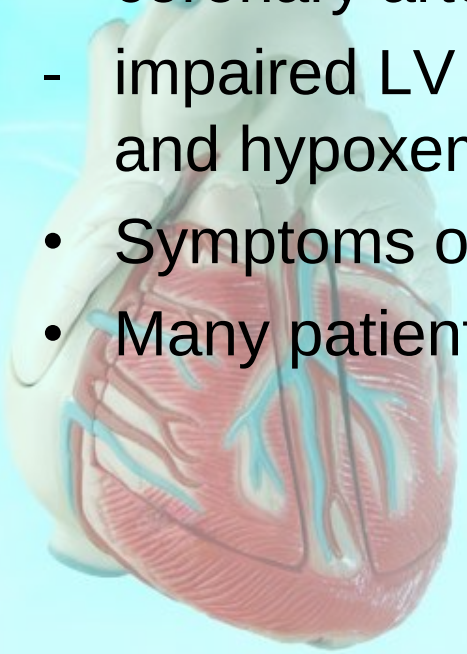
- In some patients pulmonary venous hypertension can produce severe elevations in PAP.
- Clinically it may be confusing and appear as if two separate disease processes are occurring simultaneously.
- The distinction is important, however, as treatments that are effective in PAH may make patients with pulmonary venous hypertension worse.

Left Ventricular Diastolic Dysfunction

- PH as a result of LV diastolic failure is common but often unrecognized.
- It can occur with or without LV systolic failure.
- The most common causes are:

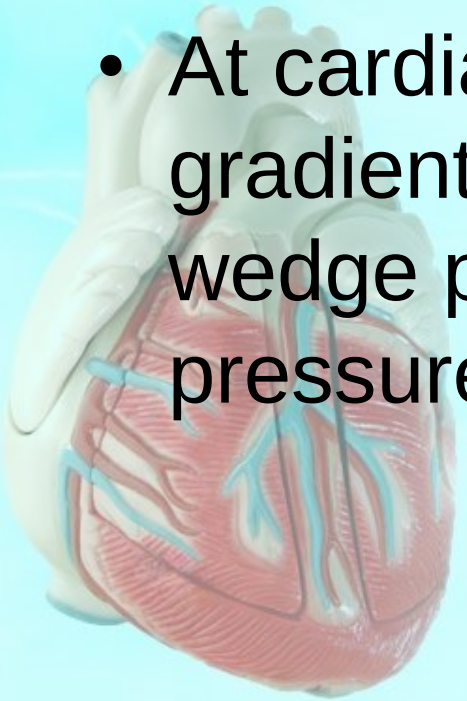
- hypertensive heart disease;
- coronary artery disease;
- impaired LV compliance related to age, diabetes, obesity, and hypoxemia.

- Symptoms of orthopnea and PND are prominent.
- Many patients improve considerably if LVEDP is lowered.



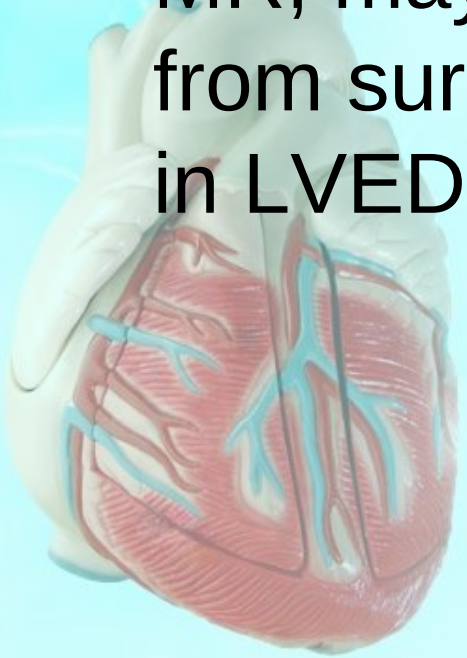
Mitral Valve Disease

- MS and MR are important causes of PH.
- These patients often have reactive pulmonary vasoconstriction resulting in marked elevations in PAP.
- At cardiac catheterization, a pressure gradient between the pulmonary capillary wedge pressure and LV end-diastolic pressure is diagnostic of mitral stenosis.



- In patients with MS, corrective surgery of the mitral valve or mitral balloon valvuloplasty predictably results in a reduction in PAP and PVR.

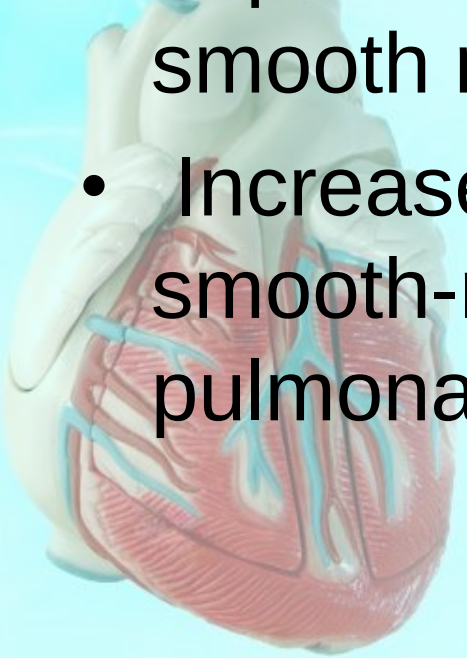
- MR, may not have as dramatic a response from surgery due to persistent elevations in LVEDP.



GROUP III

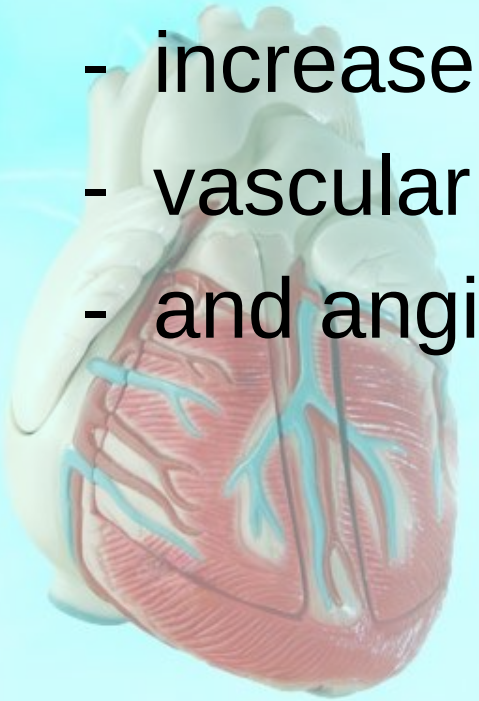
PH Associated with Lung Disease and Hypoxemia

- The mechanism of hypoxic pulmonary vasoconstriction involves the inhibition of potassium currents and membrane depolarization of pulmonary vascular smooth muscle.
- Increased calcium entry into the vascular smooth-muscle cells mediates hypoxic pulmonary vasoconstriction.

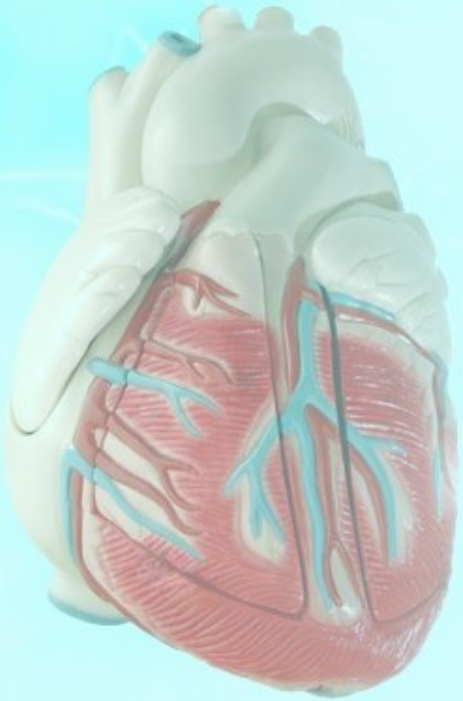


- Pulmonary vascular remodeling in response to chronic hypoxia mediated by:

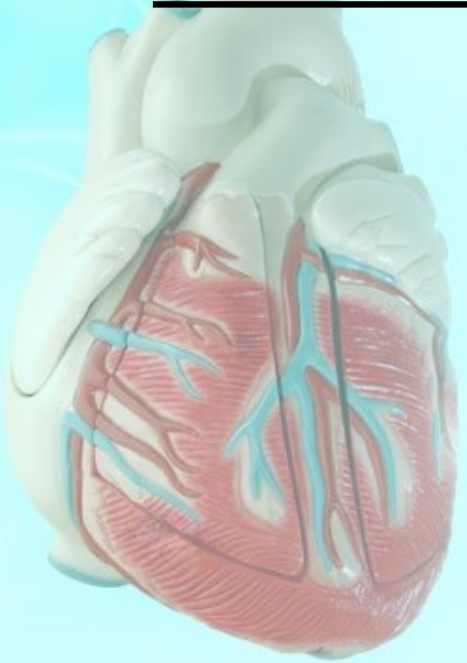
- reduction in nitric oxide production;
- increase in endothelin 1;
- increased expression of PDGF,
- vascular endothelial growth factor,
- and angiotensin II.



- Chronic hypoxia rarely leads to an increase in the systolic PAP >50 mmHg.
- Polycythemia in response to the hypoxemia is a characteristic finding.



- Hypoxia may also occur in conjunction with other causes of PH associated with more extensive vascular changes.
- Patients with chronic hypoxia who have a marked elevation in PAP should be evaluated for other causes of the PH.



Chronic Obstructive Lung Disease

- COLD is associated with mild PH in the advanced stages .
- PH has been attributed to multiple factors:

-hypoxic pulmonary vasoconstriction,

-acidemia,

-hypercapnia,

-the mechanical effects of high lung volume on pulmonary vessels,

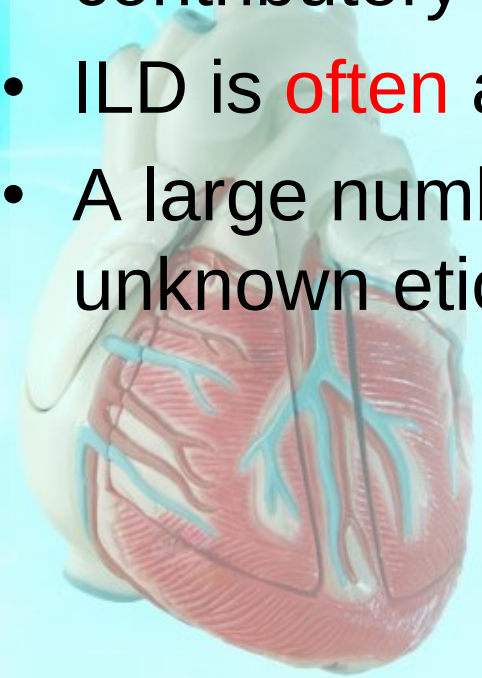
-the loss of small vessels in the vascular bed,

-and regions of emphysematous lung destruction.

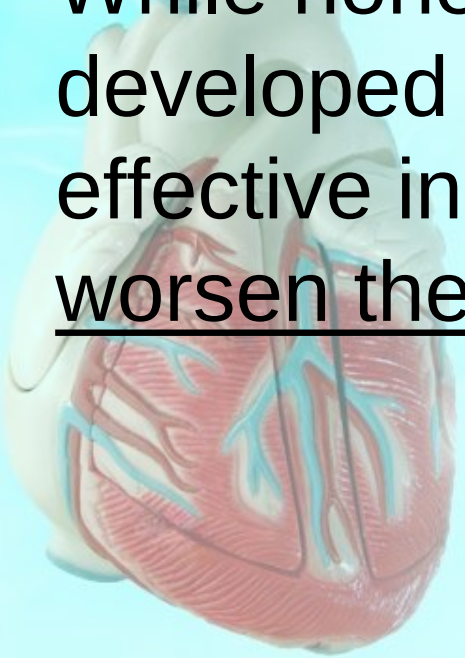
- The presence of PH in COLD confers a worse outcome.
- The only effective therapy is supplemental oxygen.
- continuous oxygen therapy relieves some of the pulmonary vasoconstriction, relieves chronic ischemia throughout the systemic and pulmonary vascular beds, and improves survival.
- Long-term oxygen therapy is indicated if the resting arterial P_{O2} <55 mmHg.

Interstitial Lung Disease

- PH from interstitial lung disease is often associated with obliteration of the pulmonary vascular bed by lung destruction and fibrosis.
- Hypoxemia and pulmonary vasculopathy can be contributory factors.
- ILD is often associated with the collagen vascular dis.
- A large number of patients have pulmonary fibrosis of unknown etiology.

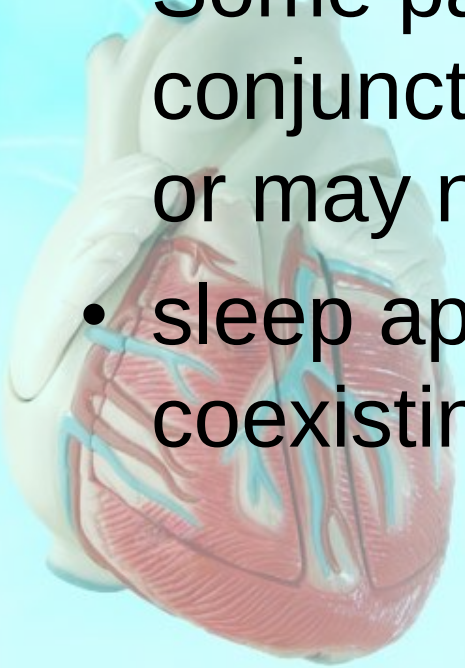


- Patients are commonly older than 50 years and report an insidious onset of progressive dyspnea and cough for months to years.
- It is uncommon for the mean PAP to exceed 40 mmHg.
- While none of the medical treatments developed for PAH have been shown to be effective in these patients, their use may worsen the hypoxemia.



Sleep-Disordered Breathing

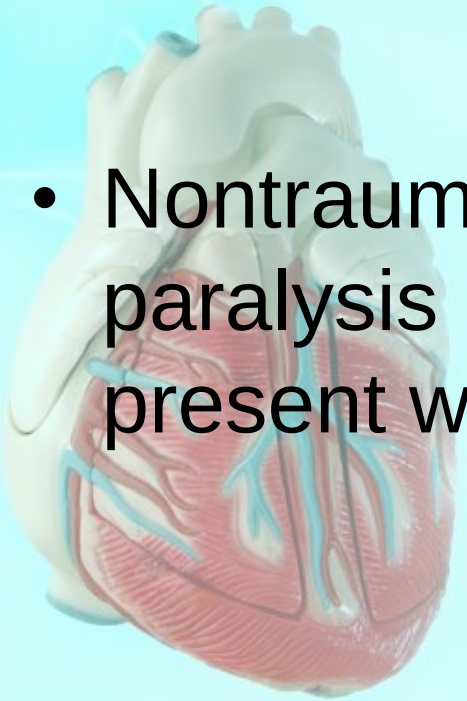
- The incidence of PH in the setting of *obstructive sleep apnea*, a common condition, appears to be <20% and is generally mild.
- Some patients, present with severe PH in conjunction with sleep apnea, which may or may not be related.
- sleep apnea and the PAH be treated as coexisting problems.



Alveolar Hypoventilation

- PH can occur in patients with chronic hypoventilation and hypoxia secondary to thoracovertebral deformities.
- Symptoms are slowly progressive and related to hypoxemia.
- In patients with advanced disease, intermittent positive-pressure breathing and supplemental oxygen have been used successfully.

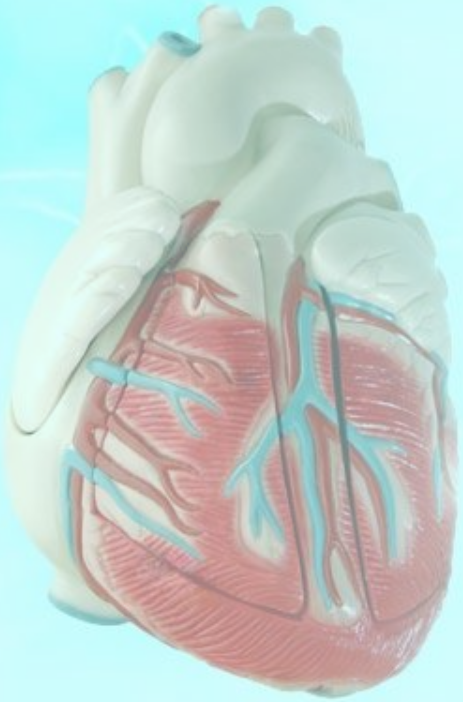
- PH secondary to hypoxemia has been reported in patients with neuromuscular disease as a result of generalized weakness of the respiratory muscles and in patients with diaphragmatic paralysis, generally a result of trauma to the phrenic nerve.



- Nontraumatic bilateral diaphragmatic paralysis may go unrecognized until they present with either respiratory failure or PH.

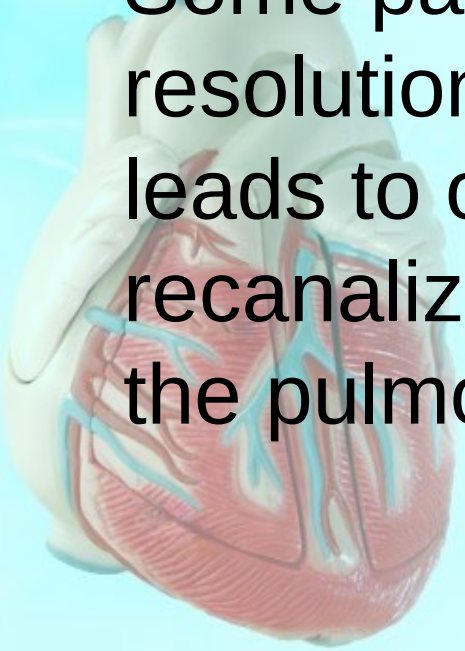
GROUP IV
PH Due to Thromboembolic Disease

- Acute Pulmonary Thromboembolism

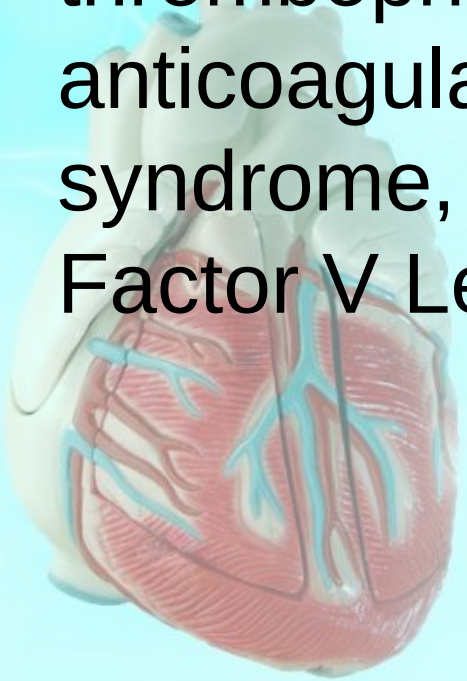


Chronic Thromboembolic Pulmonary Hypertension

- Patients appropriately treated for acute pulmonary thromboembolism with IV heparin and chronic oral warfarin therapy usually do not develop chronic PH.
- Some patients have impaired fibrinolytic resolution of the thromboembolism, which leads to organization and incomplete recanalization and chronic obstruction of the pulmonary vascular bed.

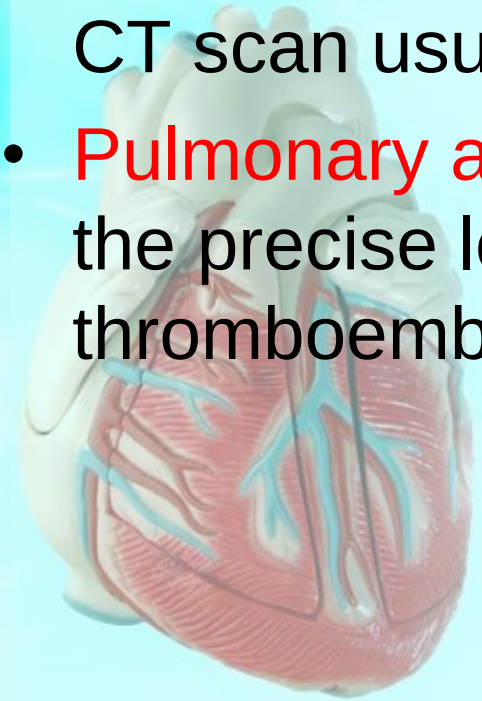


- Chronic thromboembolic PH has been well characterized and often mimics PAH.
- In many patients, the initial pulmonary thromboembolism was undetected or untreated.
- Many of these patients have underlying thrombophilic disorders, such as the lupus anticoagulant/anticardiolipin antibody syndrome, prothrombin gene mutation, or Factor V Leiden.



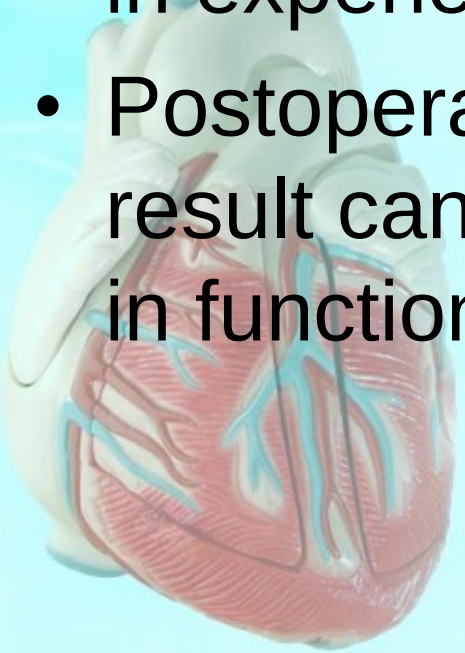
Diagnosis

- The physical examination is typical of PH but may include bruits heard over areas of the lung, representing blood flow through vessels with partial occlusion.
- A perfusion lung scan or contrast-enhanced spiral CT scan usually reveals multiple thromboemboli.
- Pulmonary angiography is necessary to determine the precise location and proximal extent of the thromboemboli, and the potential for operability.



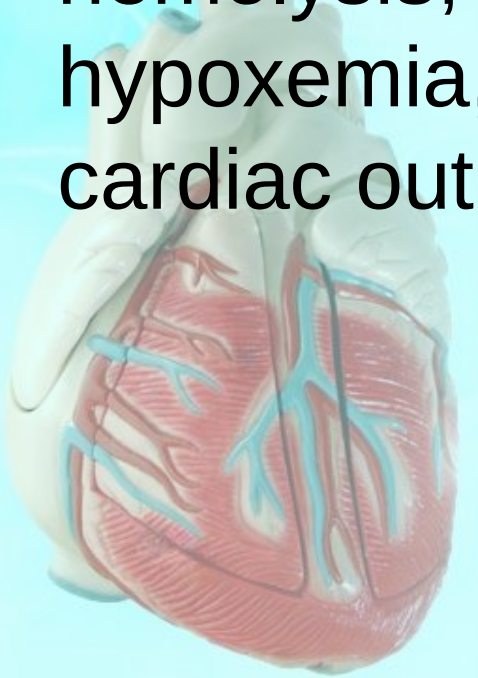
Treatment

- Thromboendarterectomy is an established surgical treatment in patients whose thrombi are accessible to surgical removal.
- The operative mortality is fairly high, at ~12% in experienced centers.
- Postoperative survivors who have a good result can expect to realize an improvement in functional class and exercise tolerance.

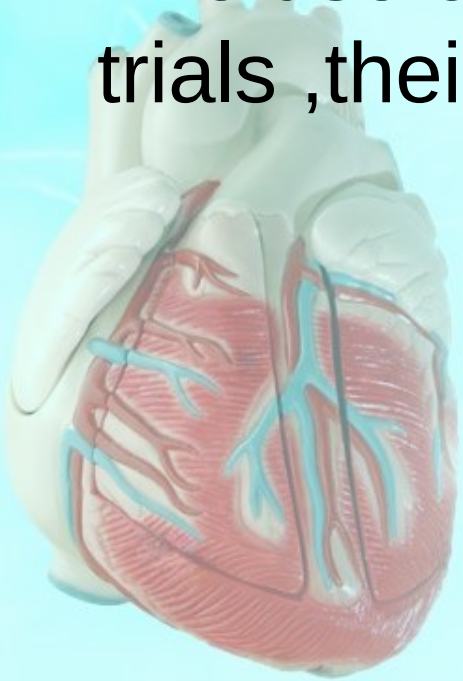


Sickle Cell Disease

- Cardiovascular system abnormalities are prominent in the clinical spectrum of sickle cell disease, including PH.
- The etiology is multifactorial, including hemolysis, impaired nitric oxide bioavailability, hypoxemia, thromboembolism, chronic high cardiac output, and chronic liver disease.

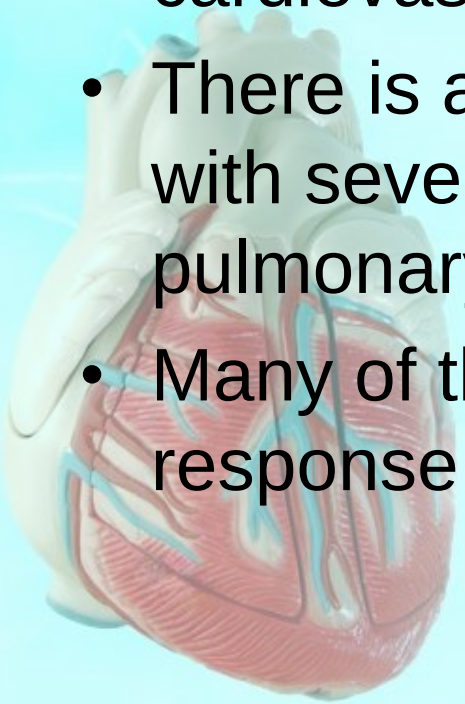


- Regardless of the mechanisms, the presence of PH in sickle cell disease is associated with a higher morbidity and mortality.
- specific therapy appears to reduce the morbidity.
- The use of drugs to treat PH is under clinical trials ,their efficacy remains unknown.



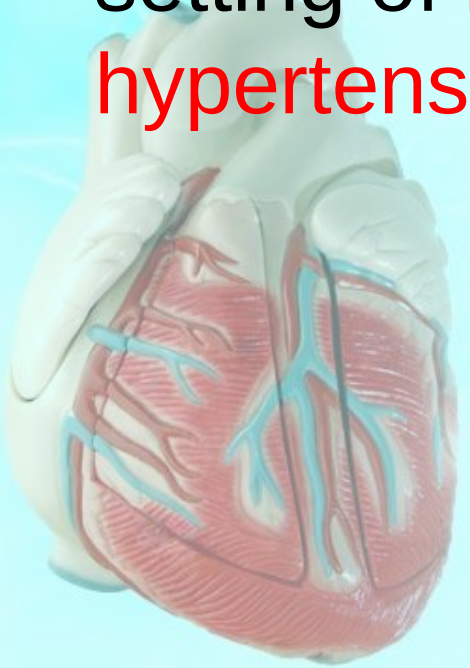
GROUP V
Other Disorders Directly Affecting Pulmonary Vasculature

- Sarcoidosis:
- Can produce severe PH as a result of chronic severe fibrocystic lung involvement, or direct cardiovascular involvement.
- There is a subset of sarcoidosis who present with severe PH believed to be due to direct pulmonary vascular involvement.
- Many of these patients exhibit a favorable response to intravenous epoprostenol therapy.

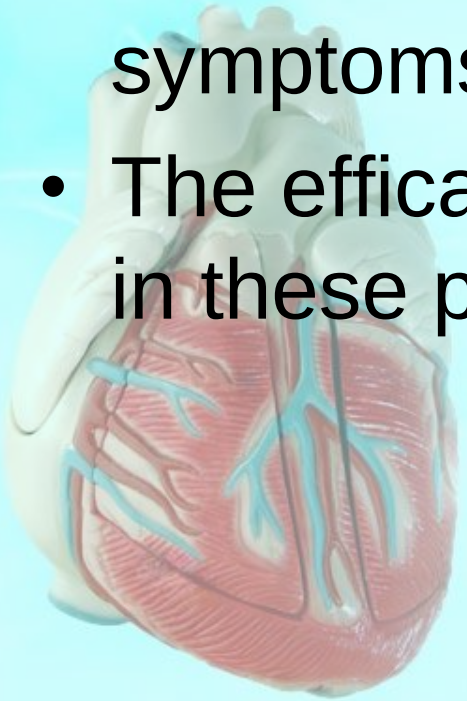


Schistosomiasis

- Although extremely rare in North America, schistosomiasis is the most common cause of PH worldwid.
- The development of PH often occurs in the setting of hepatosplenic disease and portal hypertension.

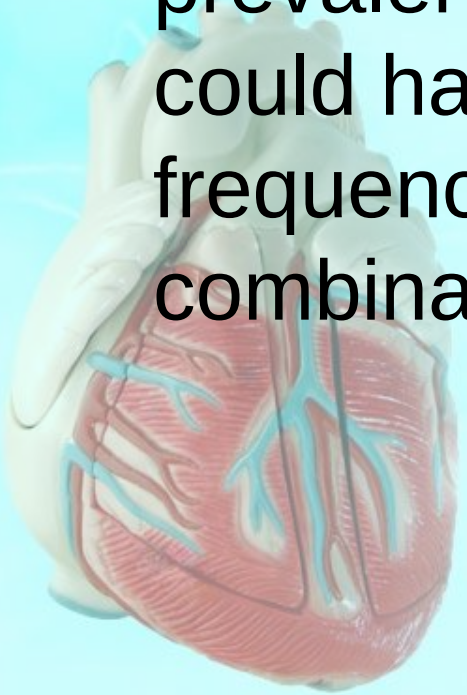


- Schistosome ova can embolize from the liver to the lungs, where they result in an inflammatory pulmonary vascular reaction and chronic changes.
- Diagnosis is confirmed by finding the parasite ova in the urine or stools of patients with symptoms, which can be difficult.
- The efficacy of therapies directed toward PH in these patients is unknown.

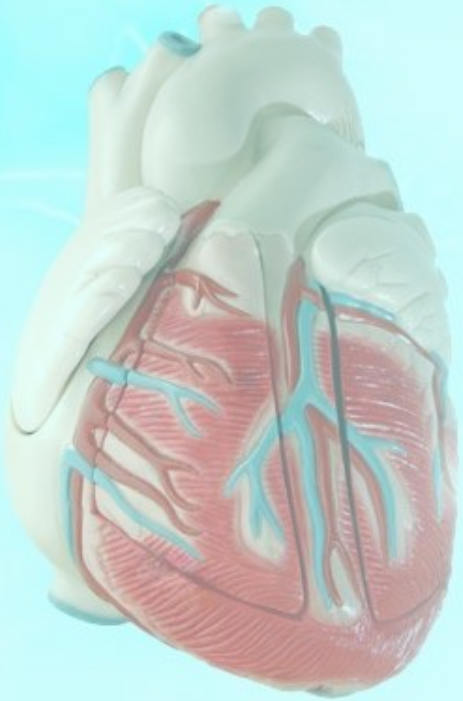


HIV Infection

- The mechanism by which HIV infection produces PH remains unknown.
- Although it is uncommon for HIV infection to result in PH, the marked rise in the prevalence of HIV infection worldwide could have a significant impact on the frequency that these entities are seen in combination.



- The evaluation and treatments are identical to those for IPAH.
- Treatment of the HIV infection does not appear to affect the severity or natural history of the underlying PH.



reference

- **Harrison‘s**
  PRINCIPLES OF INTERNAL MEDICINE
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- Chapter 250 pulmonary hypertension